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(71) Applicant *(for all designated States except US)*: ABBOTT LABORATORIES [US/US]; CHAD-0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : KLEINERT, Hollis, D. [US/US]; 1088 Pine Tree Circle North, Buffalo Grove, IL 60089 (US).

(74) Agents: GORMAN, Edward, H., Jr. et al.; Abbott Laboratories, CHAD-0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US).

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(54) Title: METHOD FOR TREATING VASCULAR DISEASES

(57) Abstract

The present invention relates to the use of renin inhibitors and to renin inhibitor compositions for treating, inhibiting, relieving or reversing vascular diseases including those vascular diseases associated with functional and/or biochemical abnormalities, and in particular peripheral vascular diseases and microvascular diseases associated with diabetes, especially diabetic retinopathy, diabetic nephropathy and diabetic neuropathy.

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METHOD FOR TREATING VASCULAR DISEASES

This is a continuation-in-part of U.S. Patent Application Serial No. 275,151, filed November 21, 1988.

Technical Field

The present invention relates to the use of renin inhibitors and to renin inhibitor compositions for treating, inhibiting, relieving or reversing vascular diseases with respect to functional and/or anatomical abnormalities, and in particular peripheral vascular diseases and microvascular diseases associated with diabetes, especially diabetic retinopathy, diabetic nephropathy and diabetic neuropathy.

Background Art

Vascular diseases are often the result of decreased perfusion in the vascular system or physical or biochemical injury to the blood vessel. One disease in which vascular diseases and their complications are very common is diabetes mellitus.

Diabetes mellitus causes a variety of physiological and anatomical irregularities, the most prominent of which is the inability of the body to

utilize glucose normally, which results in hyperglycemia. Chronic diabetes can lead to complications of the vascular system which include atherosclerosis, abnormalities involving large and medium size blood vessels (macroangiopathy) and abnormalities involving small blood vessels (microangiopathy) such as arterioles and capillaries.

The thickening and leakage of capillaries caused by diabetes primarily affect the eyes (retinopathy) and kidneys (nephropathy). The thickening and leakage of capillaries caused by diabetes are also associated with skin disorders and disorders of the nervous system (neuropathy). The eye diseases associated with diabetes are nonproliferative diabetic retinopathy, proliferative diabetic retinopathy, diabetic maculopathy, glaucoma and cataracts. It is estimated that up to 50% of diabetics will develop diabetic nephropathy, and ultimately renal failure, between 10 and 30 years from the time of onset of the diabetes.

Associations between diabetic microvascular complications and the renin-angiotensin-aldosterone system (RAAS) have been observed. Elevated plasma levels of inactive renin (prorenin) have been found in patients with incipient nephropathy, frank nephropathy, retinopathy and neuropathy. (See Luetscher, et al., Arch. Intern. Med. 148 937 (1988); Luetscher, et al., New Eng. J. Med. 312 1412 (1985); Shionoiri, et al., Curr. Therapeutics Res. 43 857 (1988); and Nakamura, et al., Acta Endocrinologica 104 216 (1983)). Chronic diabetic rats also have been found to exhibit elevated plasma prorenin. (See Ubeda, et al., Hypertension 11 339 (1988)).

Some diabetic patients have been reported to have lower than normal plasma renin activity. (See Shionoiri, et al., Curr. Therapeutics 43 857 (1988); Perez, et al., Arch. Interux. Med. 137 852 (1977); Christlieb, et al., Diabetes 23 835 (1974); and Campbell, et al., Eur. J. Clin. Invest. 6 381 (1976)). Studies in diabetic rats which also have low plasma renin activity have shown enhanced activity of the local tissue RAAS in blood vessels and the adrenal gland. (See Ubeda, et al., Hypertension 11 339 (1988)).

Suppressed plasma renin activity has not been, however, a consistent finding. Elevated plasma renin activity has been observed in diabetic patients with retinopathy and hypertension. (See Drury, et al., Clin. Endo. 16 453 (1982) and Drury, et al., Hypertension, 7 (Suppl. II) II-84 (1985)). Hypertension, if not adequately treated, will increase the incidence, severity, and rate of microvascular disease.

It is thought that high pressures in isolated vascular beds (e.g. ocular, renal) caused by localized increases in activity of the RAAS may be needed for the expression of microangiopathy. Thus an inhibitor of the renin-angiotensin-aldosterone system would be a useful therapeutic agent for diabetic microangiopathy.

Prorenin may be converted to the proteolytic enzyme renin by renal proteases or may change conformation to reveal the active proteolytic site and thus function as active renin. Renin is a highly specific enzyme which acts on only one naturally occurring substrate, angiotensinogen, which is a circulating protein. Renin acts on angiotensinogen to cleave out a fragment called angiotensin I (AI). AI itself has only slight pharmacologic activity but, after

additional cleavage by a second enzyme, angiotensin converting enzyme (ACE), forms the potent molecule angiotensin II (AII). The major pharmacological effects of AII are vasoconstriction and stimulation of the adrenal cortex to release aldosterone, a hormone which causes sodium retention. Vasoconstriction and sodium retention, which cause blood volume to increase, lead to hypertension. AII is cleaved by an aminopeptidase to form angiotensin III (AIII), which, compared to AII, is a less potent vasoconstrictor but a more potent inducer of aldosterone release.

Recently, an angiotensin converting enzyme (ACE) inhibitor has been shown to be effective in reducing albuminuria and lowering glomerular hypertension in patients with diabetic nephropathy (see Hommel, et al., Brit. Med. J. 293 467 (1986)) and, thus, it appears that inhibiting the renin-angiotensin-aldosterone system is useful for reversing or halting the progression of microangiopathy in the diabetic kidney and possibly other diabetic microvascular diseases. In addition, it has recently been shown (Science 245 186 (1989)) that ACE inhibitors have a protective and corrective effect on adverse histologic effects on blood vessels following balloon angioplasty and, therefore, inhibiting the renin-angiotensin-aldosterone system may be useful for preventing and/or reversing biochemical or physical injury to blood vessels.

However, ACE acts on several substrates other than angiotensin I (AI), most notably the kinins which cause such undesirable side effects as pain, "leaky" capillaries, prostaglandin release and a variety of behavorial and neurologic effects. Further, ACE

inhibition leads to the accumulation of AI. Although AI has much less vasoconstrictor activity than AII, its presence may negate some of the hypotensive effects of the blockade of AII synthesis.

Renin inhibitors have been disclosed as agents for treating systemic hypertension and there are no known side effects which result when renin is inhibited from acting on its substrate.

Disclosure of the Invention

It has now been discovered that renin inhibitors are useful for the prevention, treatment, inhibition or reversal of vascular diseases including those vascular diseases associated with functional and/or anatomical abnormalities, and in particular peripheral vascular diseases and microvascular diseases associated with diabetes, especially diabetic retinopathy, diabetic nephropathy and diabetic neuropathy.

Examples of renin inhibitors and the methods for preparing the renin inhibitors include, but are not limited to, those disclosed in the following references, which are hereby incorporated by reference.

References Disclosing Renin Inhibiting Compounds

1. Luly, et al., U.S. Patent No. 4,652,551, issued March 24, 1987.

2. Luly, et al., U.S. Patent No. 4,645,759, issued February 24, 1987.

3. Luly, et al., U.S. Patent No. 4,680,284, issued July 14, 1987.

4. Luly, et al., U.S. Patent No. 4,725,583, issued February 16, 1988.

5. Luly, et al., U.S. Patent No. 4,725,584, issued February 16, 1988.

6. Riniker, et al., U.S. Patent No. 4,595,677 issued June 17, 1986.

7. Fuhrer, et al., U.S. Patent No. 4,613,676, issued September 23, 1986.

8. Buhlmayer, et al., U.S. Patent No. 4,727,060, issued February 23, 1988.

9. Buhlmayer, et al., U.S. Patent No. 4,758,584, issued July 19, 1988.

10. Iizuka, et al., U.S. Patent No. 4,656,269, issued April 7, 1987.

11. Iizuka, et al., U.S. Patent No. 4,711,958, issued December 8, 1987.

12. Veber, et al., U.S. Patent No. 4,384,994, issued May 24, 1983.

13. Boger, et al., U.S. Patent No. 4,470,971, issued September 11, 1984.

14. Boger, et al., U.S. Patent No. 4,477,440, issued October 16, 1984.

15. Boger, et al., U.S. Patent No. 4,477,441, issued October 16, 1984.

16. Veber, et al., U.S. Patent No. 4,479,941, issued October 30, 1984.

17. Boger, et al., U.S. Patent No. 4,485,099, issued November 27, 1984.

18. Boger, et al., U.S. Patent No. 4,668,663, issued May 26, 1987.

19. Boger, et al., U.S. Patent No. 4,665,052, issued May 12, 1987.

20. Bock, et al., U.S. Patent No. 4,636,491, issued November 3, 1987.

21. Boger, et al., U.S. Patent No. 4,661,473, issued April 28, 1987.

22. Bock, et al., U.S. Patent No. 4,663,310, issued May 5, 1987.

23. Evans, et al., U.S. Patent No. 4,609,641, issued September 2, 1986.

24. Evans, et al., U.S. Patent No. 4,665,055, issued May 12, 1987.

25. Boger, et al., U.S. Patent No. 4,668,770, issued May 26, 1987.

26. Boger, U.S. Patent No. 4,743,584, issued May 10, 1988.

27. Raddatz, et al., U.S. Patent No. 4,666,888, issued May 19, 1987.

28. Holzemann, et al., U.S. Patent No. 4,709,010, issued November 24, 1987.

29. Raddatz, et al., U.S. Patent No. 4,721,776, issued January 26, 1988.

30. Raddatz, et al., U.S. Patent No. 4,755,592, issued July 5, 1988.

31. Hoover, U.S. Patent No. 4,599,198, issued July 8, 1986.

32. Bindra, et al., U.S. Patent No. 4,729,985, issued March 8, 1988.

33. Hoover, U.S. Patent No. 4,668,769, issued May 26, 1987.

34. Bindra, et al., U.S. Patent No. 4,749,687, issued June 7, 1988.

35. Matsueda, et al., U.S. Patent No. 4,548,926, issued October 22, 1985.

36. Matsueda, et al., U.S. Patent No. 4,698,329, issued October 6, 1987.

37. Cazaubon, et al., U.S. Patent No. 4,481,192, issued November 6, 1984.

38. Wagnon, et al., U.S. Patent No. 4,725,580, issued February 16, 1988.

39. Hansen, et al., U.S. Patent No. 4,510,085, issued April 9, 1985.

40. Hansen, et al., U.S. Patent No. 4,514,332, issued April 30, 1985.

41. Baran, et al., U.S. Patent No. 4,657,931, issued April 14, 1987.

42. Hansen, et al., U.S. Patent No. 4,722,922, issued February 2, 1988.

43. Ryono, et al., U.S. Patent No. 4,616,088, issued October 7, 1986.

44. Ryono, et al., U.S. Patent No. 4,665,193, issued May 12, 1987.

45. Ryono, et al., U.S. Patent No. 4,629,724, issued December 16, 1986.

46. Natarajan, et al., U.S. Patent No. 4,757,050, issued July 12, 1988.

47. Gordon, U.S. Patent No. 4,749,781, issued June 7, 1988.

48. Szelke, et al., U.S. Patent No. 4,609,643, issued September 2, 1986.

49. Szelke, et al., U.S. Patent No. 4,650,661, issued March 17, 1987.

50. Szelke, et al., U.S. Patent No. 4,713,445, issued December 15, 1987.

51. Thaisrivongs, U.S. Patent No. 4,705,846, issued November 10, 1987.

52. Hudspeth, et al., U.S. Patent No. 4,735,933, issued April 5, 1988.

53. Hudspeth, et al., U.S. Patent No. 4,743,585, issued May 10, 1988.

54. Sham, U.S. Patent No. 4,826,958, issued May 2, 1989.

55. Rosenberg, et al., U.S. Patent No. 4,857,507, issued August 15, 1989.

56. Luly, et al., U.S. Patent No. 4,826,815, issued May 2, 1989.

57. Rosenberg, et al., U.S. Patent No. 4,837,204, issued June 6, 1989.

58. Luly, et al., U.S. Patent No. 4,845,079, issued July 4, 1989.

59. Bender, et al., U.S. Patent No. 4,818,748, issued April 4, 1989.

60. Kleinman, et al., U.S. Patent No. 4,729,985, issued March 8, 1988.

61. Hoover, et al., U.S. Patent No. 4,814,342, issued March 21, 1989.

62. Wagnon, et al., U.S. Patent No. 4,746,648, issued May 24, 1988.

63. Natarajan, et al., U.S. Patent No. 4,757,050, issued July 12, 1988.

64. Patel, U.S. Patent No. 4,820,691, issued April 11, 1989.

65. Kaltenbronn, et al., U.S. Patent No. 4,804,743, issued February 14, 1989.

66. Pinori, et al., U.S. Patent No. 4,560,505, issued December 24, 1985.

67. Yamato, et al., U.S. Patent No. 4,683,220, issued July 28, 1987.

68. Boger, et al., U.S. Patent No. 4,812,442, issued March 14, 1989.

69. Patchett, et al., U.S. Patent No. 4,839,357, issued June 13, 1989.

70. Boger, et al., U.S. Patent No. 4,812,442, issued March 14, 1989.

71. Veber, et al., U.S. Patent No. 4,478,826, issued October 23, 1984.

72. Raddatz, et al., U.S. Patent No. 4,812,555, issued March 14, 1989.

73. Wagnon, et al., U.S. Patent No. 4,840,935, issued June 20, 1989.

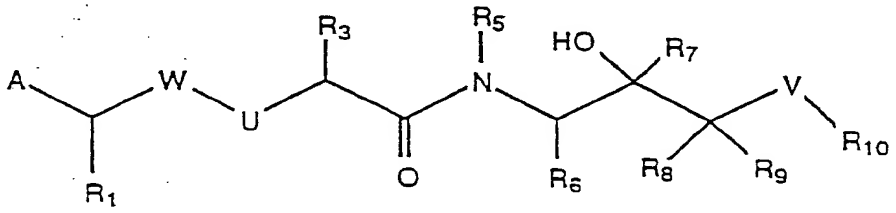
74. Iizuka, et al., U.S Patent No. 4,841,067, issued June 20, 1989.

75. Raddatz, et al., U.S. Patent No. 4,829,053, issued May 9, 1989.

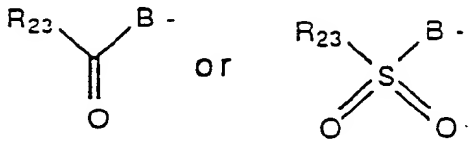
Preferred renin inhibitors and methods for making them include those disclosed in U.S. Patent No. 4,826,815, issued May 2, 1989; U.S. Patent No. 4,857,507, issued August, 15, 1989; U.S. Patent No. 4,826,958, issued May 2, 1989; U.S. Patent No. 4,837,204, issued June 6, 1989; U.S. Patent No. 4,845,079 issued July 4, 1989, which are hereby incorporated by reference. Preferred renin inhibitors and methods for making them also include those disclosed in copending U.S. patent applications, USSN 403,906, filed September 1, 1989; USSN 231,869, filed August 16, 1988 (EP0307837, published March 22, 1989); USSN 132,356, filed December 18, 1987 (WO88/05050, published July 14, 1988); PCT/US89/04385, filed October 3, 1989; and PCT/US89/04649, filed October 18, 1989, which are hereby incorporated by reference.

The preferred renin inhibiting compounds of this invention are selected from the group consisting of compounds of the formula:

(1).



wherein A is hydrogen, loweralkyl, arylalkyl, $-OR_{20}$ wherein R_{20} is hydrogen, or loweralkyl, $-NR_{21}R_{22}$ wherein R_{21} and R_{22} are independently selected from hydrogen and loweralkyl;
or A is



wherein B is NH, O, CH_2 or $NHCH_2$; and R_{23} is loweralkyl, alkoxy, arylalkoxy, arylalkoxyalkyl, amino, alkylamino, dialkylamino, carboxyalkyl, alkoxycarbonyalkyl, (dihydroxyalkyl)(alkyl)amino, aminoalkyl, N-protected aminoalkyl, (heterocyclic)alkyl, or a substituted or unsubstituted heterocyclic;

W is C=O, CH_2 or CHOH;

U is CH_2 or NR_2, wherein R_2 is hydrogen or loweralkyl, provided that when W is CHOH then U is CH_2;

R_1 is loweralkyl, cycloalkylalkyl, benzyl, 4-methoxybenzyl, 4-hydroxybenzyl, halobenzyl, (1-naphthyl)methyl, (2-naphthyl)methyl, (4-imidazolyl)methyl, (alpha,alpha)-dimethylbenzyl, 1-benzyloxyethyl, phenethyl, phenoxy, thiophenoxy or anilino; provided that when R_1 is phenoxy, thiophenoxy or anilino, then B is CH_2 or A is hydrogen;

R_3 is loweralkyl, (thioalkoxy)alkyl, benzyl or heterocyclic ring substituted methyl;

R_5 is hydrogen or loweralkyl;

R_6 is loweralkyl, cycloalkylmethyl, or benzyl;

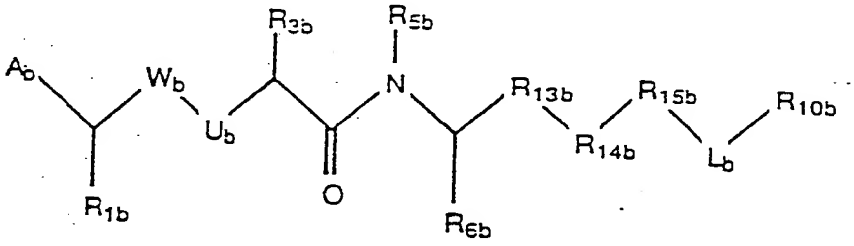
R_7, R_8 and R_9 are hydrogen or loweralkyl

and may be the same or different;

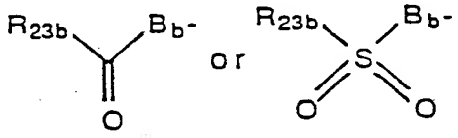
V is NH, O, S, SO, SO_2, or CH_2;

R_{10} is loweralkyl, cycloalkyl, (cycloalkyl)alkyl, aryl, arylalkyl or an N-protecting group, or V and R_{10} taken together are N_3; with the proviso that R_{10} may be an N-protecting group only when V is NH;

(2).



wherein A_b is hydrogen, loweralkyl, arylalkyl; OR_{20b} or SR_{20b} wherein R_{20b} is hydrogen, loweralkyl or aminoalkyl, $NR_{21b}R_{22b}$ wherein R_{21b} and R_{22b} are independently selected from hydrogen, loweralkyl, aminoalkyl, cyanoalkyl and hydroxyalkyl;
or A_b is



wherein B_b is NH, alkylamino, S, O, CH_2, or CHOH; and R_{23b} is loweralkyl, cycloalkyl, aryl, arylalkyl, alkoxy, alkenyloxy, hydroxyalkoxy, dihydroxyalkoxy, arylalkoxy, arylalkoxyalkyl, amino, alkylamino, dialkylamino, (hydroxyalkyl)(alkyl)amino,

(dihydroxyalkyl)(alkyl)amino, aminoalkyl, N-protected aminoalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, (N-protected)(alkyl)aminoalkyl, dialkylaminoalkyl, (heterocyclic)alkyl, or a substituted or unsubstituted heterocyclic;

W_b is C=O or CHOH;

U_b is CH_2 or NR_{2b}, wherein R_{2b} is hydrogen or loweralkyl, provided that when W_b is CHOH then U_b is CH_2;

R_{1b} is loweralkyl, cycloalkylalkyl, benzyl, 4-methoxybenzyl, 4-hydroxybenzyl, halobenzyl, (1-naphthyl)methyl, (2-naphthyl)methyl, (4-imidazolyl)methyl, (alpha,alpha)-dimethylbenzyl, 1-benzyloxyethyl, phenethyl, phenoxy, thiophenoxy or anilino; provided that when R_{1b} is phenoxy, thiophenoxy or anilino, then B_b is CH_2 or CHOH or A_b is hydrogen;

R_{3b} is loweralkyl, loweralkenyl, benzyl or heterocyclic ring substituted methyl;

R_{5b} is hydrogen or loweralkyl;

R_{6b} is loweralkyl, cycloalkylmethyl, or benzyl;

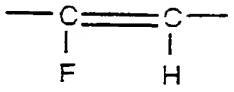
R_{10b} is loweralkyl, cycloalkyl, (cycloalkyl)alkyl, aryl, arylalkyl or an N-protecting group, or L_b and R_{10b} taken together can be N_3, with the proviso that when L_b is NH then R_{10b} is an N-protecting group;

R_{13b} is CHOH or CO;

R_{14b} is CH_2, CF_2 or CF with the proviso that when R_{13b} is CO then R_{14b} is CF_2;

R_{15b} is CH_2, CHR_{25b} wherein R_{25b} is loweralkyl, cycloalkyl, cycloalkylalkyl, aryl or

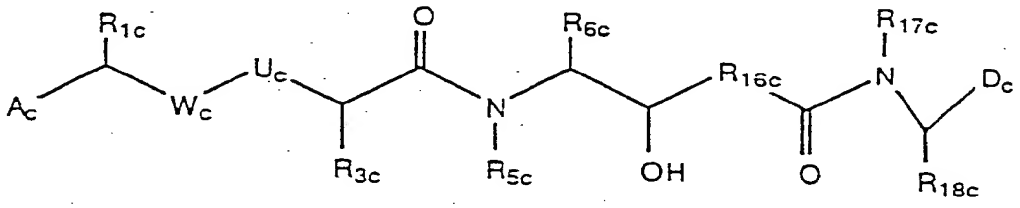
arylalkyl, or R_{14b} and R_{15b} taken together can be



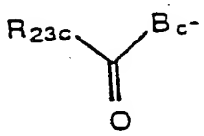
with the proviso that when R_{14} is CF_2 then R_{15} is CH_2;

L_b is O, S, SO, SO_2, NR_{26b} wherein R_{26b} is hydrogen or loweralkyl, or $NR_{27b}C(O)$ wherein R_{27b} is hydrogen or loweralkyl;

(3).



wherein A_c is



wherein B_c is NH, or CH_2; and R_{23c} is loweralkyl, alkoxy, or a substituted or unsubstituted heterocyclic;

W_c is C=O;

U_c is NR_{2c}, wherein R_{2c} is hydrogen or loweralkyl;

R_{1c} is loweralkyl, cycloalkylalkyl, benzyl, 4-methoxybenzyl, 4-hydroxybenzyl, halobenzyl, (1-naphthyl)methyl, (2-naphthyl)methyl, (4-imidazolyl)methyl, (alpha,alpha)-dimethylbenzyl, 1-benzyloxyethyl, or phenethyl;

R_{3c} is loweralkyl, benzyl or heterocyclic ring substituted methyl;

R_{5c} is hydrogen or loweralkyl;

R_{6c} is loweralkyl, cycloalkylmethyl, benzyl, or CH_2R_{24c}, where R_{24c} is selected from 1,3-dioxan-2-yl; 1,3-dioxolan-2-yl, 1,3-dithiolan-2-yl or 1,3-dithian-2-yl;

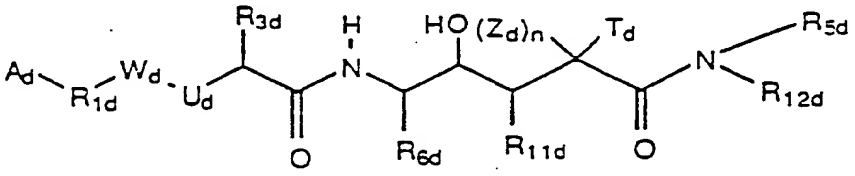
R_{16c} is CH_2, CF_2 or CHR_{63c} where R_{63c} is loweralkyl, hydroxy, hydroxyalkyl, alkoxy, allyl, arylalkoxy or thioalkyl;

R_{17c} is hydrogen or loweralkyl;

R_{18c} is loweralkyl or lipophilic or aromatic amino acid side chain;

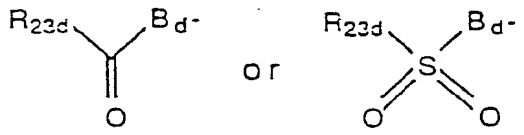
D_c is hydrogen, loweralkyl or $-CH_2OR_{28c}$, wherein R_{28c} is hydrogen, loweralkyl or arylalkyl;

(4).



wherein A_d is hydrogen, loweralkyl, arylalkyl, $-OR_{20d}$ or $-SR_{20d}$ wherein R_{20d} is hydrogen, loweralkyl or aminoalkyl, $-NR_{21d}R_{22d}$ wherein R_{21d}

and R_{22d} are independently selected from hydrogen, loweralkyl, aminoalkyl, cyanoalkyl and hydroxyalkyl; or A_d is



wherein B_d is NH, alkylamino, S, O, CH_2, or $NHCH_2$, and R_{23d} is loweralkyl, cycloalkyl, aryl, arylalkyl, alkoxy, alkenyloxy, hydroxyalkoxy, dihydroxyalkoxy, arylalkoxy, arylalkoxyalkyl, amino, alkylamino, dialkylamino, (hydroxyalkyl)(alkyl)amino, ((dialkylamino)alkyl)(alkyl)amino, (dihydroxyalkyl)(alkyl)amino, aminoalkyl, N-protected aminoalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, (N-protected)(alkyl)aminoalkyl, dialkylaminoalkyl, (heterocyclic)alkyl, or a substituted or unsubstituted heterocyclic;

W_d is C=O or CHOH;

U_d is CH_2 or NR_{2d}, wherein R_{2d} is hydrogen or loweralkyl, provided that when W_d is CHOH then U_d is CH_2;

R_{1d} is CHR_{24d} wherein R_{24d} is loweralkyl, cycloalkylalkyl, benzyl, 4-methoxybenzyl, 4-hydroxybenzyl, halobenzyl, (1-naphthyl)methyl, (2-naphthyl)methyl, (4-imidazoyl)methyl, (alpha, alpha)-dimethylbenzyl, 1-benzyloxyethyl, or phenethyl, or R_{1d} is $C=CHR_{25d}$ wherein R_{25d} is aryl;

R_{3d} is loweralkyl, alkenyl, benzyl or heterocyclic ring substituted methyl;

R_{5d} is hydrogen or loweralkyl;

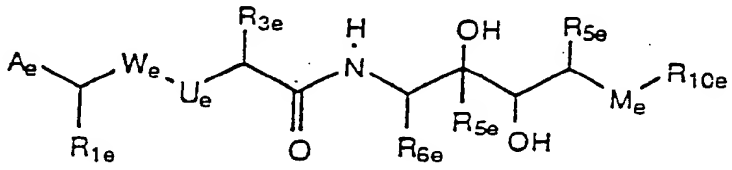
R_{6d} is loweralkyl, cycloalkylmethyl, or benzyl;

R_{11d} is hydrogen or hydroxy;

n is 0 or 1; when n is 0 then T_d is alkylidene or alkylidene oxide; and when n is 1 then Z_d is hydrogen or hydroxy and T_d is loweralkyl, hydroxyalkyl, aminoalkyl, haloalkyl, or azidoalkyl;

R_{12d} is hydrogen, loweralkyl, cycloalkylalkyl, arylalkyl, aminoalkyl, or dialkylaminoalkyl;

(5).



wherein A_e is hydrogen, loweralkyl, arylalkyl, $-OR_{20e}$ or $-SR_{20e}$ wherein R_{20e} is hydrogen, loweralkyl or aminoalkyl, $-NR_{21e}R_{22e}$ wherein R_{21e} and R_{22e} are independently selected from hydrogen, loweralkyl, aminoalkyl, cyanoalkyl and hydroxyalkyl; or A_e is

wherein B_e is NH, alkylamino, S, O, CH_2, or CHOH; and R_{23e} is loweralkyl, cycloalkyl, aryl, arylalkyl,

alkoxy, alkenyloxy, hydroxyalkoxy, dihydroxyalkoxy, arylalkoxy, arylalkoxyalkyl, amino, alkylamino, dialkylamino, (hydroxyalkyl)(alkyl)amino, (dihydroxyalkyl)(alkyl)amino, aminoalkyl, N-protected aminoalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, (N-protected)(alkyl)aminoalkyl, dialkylaminoalkyl, (heterocyclic)alkyl, or a substituted or unsubstituted heterocyclic;

W_e is C=O;

U_e is NR_{2e}, wherein R_{2e} is hydrogen or loweralkyl;

R_{1e} is loweralkyl, cycloalkylalkyl, benzyl, 4-methoxybenzyl, 4-hydroxybenzyl, halobenzyl, (1-naphthyl)methyl, (2-naphthyl)methyl, (4-imidazolyl)methyl, (alpha,alpha)-dimethylbenzyl, 1-benzyloxyethyl, phenethyl, phenoxy, thiophenoxy or anilino, provided that when R_{1e} is phenoxy, thiophenoxy or anilino, then B_e is CH_2 or CHOH or A_e is hydrogen;

R_{3e} is loweralkyl, benzyl or heterocyclic ring substituted methyl;

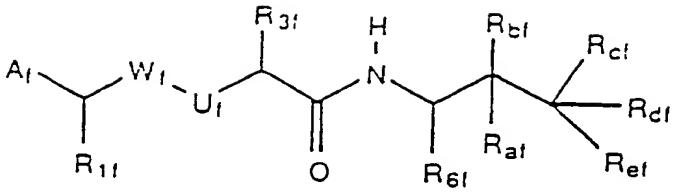
R_{5e} is hydrogen or loweralkyl;

R_{6e} is loweralkyl, cycloalkylmethyl, or benzyl;

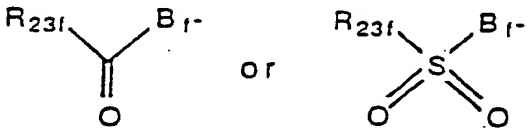
M_e is O, NH or S;

R_{10e} is hydrogen, loweralkyl, cycloalkyl, (cycloalkyl)alkyl, aryl, arylalkyl or an N-protecting group;

(6).



wherein A_f is hydrogen, loweralkyl, arylalkyl, $-OR_{10f}$ or $-SR_{10f}$ wherein R_{10f} is hydrogen, loweralkyl or aminoalkyl, $-NR_{11f}R_{12f}$ wherein R_{11f} and R_{12f} are independently selected from hydrogen, loweralkyl, aminoalkyl, cyanoalkyl, hydroxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, (amino)carboxyalkyl, ((N-protected)amino)carboxyalkyl, (alkylamino)carboxyalkyl, ((N-protected)alkylamino)carboxyalkyl, (dialkylamino)carboxyalkyl, (amino)alkoxycarbonylalkyl, ((N-protected)amino)alkoxycarbonylalkyl, (alkyamino)alkoxycarbonylalkyl, ((N-protected)alkylamino)alkoxycarbonylalkyl and (dialkylamino)alkoxycarbonylalkyl;
or A_f is



wherein B_f is NH, alkylamino, S, O, CH_2 or CHOH and R_{13f} is loweralkyl, cycloalkyl, aryl, arylalkyl, alkoxy, alkenyloxy, hydroxyalkoxy, dihydroxyalkoxy, arylalkoxy, arylalkoxyalkyl, amino, alkylamino,

dialkylamino, (hydroxyalkyl)(alkyl)amino, (dihydroxyalkyl)(alkyl)amino, aminoalkyl, N-protected-aminoalkyl, alkylaminoalkyl, (N-protected)(alkyl)aminoalkyl, dialkylaminoalkyl, carboxyalkoxyalkyl, (alkoxycarbonyl)alkoxyalkyl, carboxyalkyl, carboxyalkylamino, alkoxycarbonylalkyl, alkoxycarbonyalkylamino, (amino)carboxyalkyl, (amino)carboxyalkylamino, ((N-protected)amino)carboxyalkyl, ((N-protected)amino)-carboxyalkyamino, (alkylamino)carboxyalkyl, (alkylamino)carboxyalkylamino, ((N-protected)alkylamino)-carboxyalkyl, ((N-protected)alkylamino)carboxyalkylamino, (dialkylamino)carboxyalkyl, (dialkylamino)carboxyalkylamino, (amino)alkoxycarbonylalkyl, (amino)alkoxycarbonylalkylamino, ((N-protected)amino)alkoxycarbonylalkyl, ((N-protected)amino)- alkoxycarbonylalkylamino, (alkylamino)alkoxycarbonylalkyl, (alkylamino)alkoxycarbonylalkylamino, ((N-protected)alkylamino)- alkoxycarbonylalkyl, ((N-protected)alkylamino)alkoxycarbonyl- alkylamino, (dialkylamino)alkoxycarbonylalkyl, (dialkylamino)alkoxycarbonylalkylamino, aminocycloalkyl, aminoalkylamino, dialkylaminoalkyl(alkyl)amino, arylalkylamino, arylalkyl(alkyl)amino, alkoxyalkyl(alkyl)amino, (polyalkyoxy)-alkyl(alkyl)amino, di-(alkoxyalkyl)amino, di-(hydroxyalkyl)amino, di-((polyalkoxy)alkyl)amino, polyalkoxy, (polyalkoxy)alkyl, (heterocyclic)alkyl or a substituted or unsubstituted heterocyclic wherein saturated heterocyclics may be unsubstituted,

monosubstituted or disubstituted with hydroxy, oxo, amino, alkylamino, dialkylamino, alkoxy, polyalkoxy or loweralkyl; unsaturated heterocyclics may be unsubstituted or monosubstituted with hydroxy, amino, alkylamino, dialkylamino, alkoxy, polyalkoxy or loweralkyl;

W_f is C=O or CHOH;

U_f is CH_2 or NR_2, provided that when W_f is CHOH then U_f is CH_2;

R_{1f} is loweralkyl, cycloalkylmethyl, benzyl, 4-methoxybenzyl, halobenzyl, (1-naphthyl)methyl, (2-naphthyl)methyl, (4-imidazolyl)methyl, (alpha,alpha)-dimethylbenzyl, 1-benzyloxyethyl, phenethyl, phenoxy, thiophenoxy or anilino; provided that when R_{1f} is phenoxy, thiophenoxy or anilino, then B_f is CH_2 or CHOH or A_f is hydrogen;

R_{2f} is hydrogen or loweralkyl;

R_{3f} is loweralkyl, loweralkenyl, ((alkoxy)alkoxy)loweralkyl, (thioalkoxy)alkyl, benzyl or heterocyclic ring substituted methyl;

R_{6f} is loweralkyl, cycloalkylmethyl or benzyl;

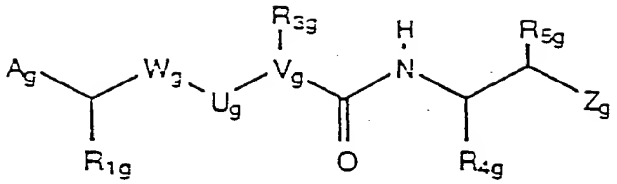
R_{af} is vinyl, formyl, hydroxymethyl or hydrogen;

R_{df} is hydrogen or loweralkyl;

R_{bf} and R_{ef} are independently selected from OH and NH_2; and

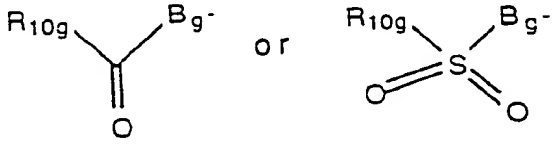
R_{cf} is hydrogen, loweralkyl, vinyl or arylalkyl;

(7).



wherein A_g is hydrogen, loweralkyl, aminoalkyl, (alkyl)aminoalkyl, dialkylaminoalkyl, (alkoxy)aminoalkyl, (alkoxy)(alkyl)aminoalkyl, phenylalkyl, (substituted phenyl)alkyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkoxy, loweralkyl, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide, naphthylalkyl, (substituted naphthyl)alkyl wherein the naphthyl ring is substituted with one, two or three substituents independently selected from loweralkoxy, loweralkyl, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide, substituted or unsubstituted heterocyclic, where saturated heterocyclics may be unsubstituted, monosubsituted or disubstituted with hydroxy, oxo, amino, alkylamino, dialkylamino, alkoxy, polyalkoxy, loweralkyl, haloalkyl or polyhaloalkyl; unsaturated heterocyclics may be unsubstituted or monosubstituted with hydroxy, amino, alkylamino, dialkylamino, alkoxy, polyalkoxy, loweraklyl, haloalkyl or polyhaloalkyl, or A_g is (unsubstituted heterocyclic)alkyl or (substituted heterocyclic)alkyl wherein unsubstituted or substituted

heterocyclic is as defined above, or A_g is $-OR_{7g}$ or $-SR_{7g}$ wherein R_{7g} is hydrogen, loweralkyl, aminoalkyl, (alkyl)aminoalkyl, dialkylaminoalkyl, (alkoxy)aminoalkyl, (alkoxy)(alkyl)aminoalkyl, phenylalkyl, (substituted phenyl)alkyl wherein substituted phenyl is as defined above, naphthylalkyl, (substituted naphthyl)alkyl wherein the substituted naphthyl is as defined above, substituted or unsubstituted heterocyclic as defined above, (unsubstituted heterocyclic)alkyl or (substituted heterocyclic)alkyl wherein unsubstituted or substituted heterocyclic is as defined above, (unsubstituted heterocyclic)C(O)- or (substituted heterocyclic)C(O)- wherein unsubstituted or substituted heterocyclic is as defined above; or A_g is $-NR_{8g}R_{9g}$ wherein R_{8g} and R_{9g} are independently selected from hydroxy, alkoxy, loweralkyl, aminoalkyl, cyanoalkyl and hydroxyalkyl; or A_g is



wherein B_g is NH, alkylamino, S, O, CH_2, $NHCH_2$ or $CH(OR_{52g})$ wherein R_{52g} is hydrogen, loweralkyl or loweralkylcarbonyl, and R_{10g} is hydrogen, loweralkyl, cycloalkyl, phenyl, substituted phenyl as defined above, naphthyl, substituted naphthyl as defined above, alkoxy, alkenyloxy, hydroxyalkoxy, dihydroxyalkoxy, phenylalkoxy, (substituted phenyl)alkoxy wherein substituted phenyl is as defined above, naphthylalkoxy, (substituted naphthyl)alkoxy wherein substituted

naphthyl is as defined above, phenylalkoxyalkyl, (substituted phenyl)alkoxyalkyl wherein substituted phenyl is as defined above, naphthylalkoxyalkyl, (substituted naphthyl)alkoxyalkyl wherein substituted naphthyl is as defined above, thioalkoxyalkyl, loweralkylsulfinylalkyl, loweralkylsulfonylalkyl, phenylthioalkyl, (substituted phenyl)thioalkyl wherein substituted phenyl is as defined above, naphthylthioalkyl, (substituted naphthyl)thioalkyl wherein substituted naphthyl is as defined above, phenylsulfonylalkyl, (substituted phenyl)sulfonylalkyl wherein substituted phenyl is as defined above, naphthylsulfonylalkyl, (substituted naphthyl)sulfonylalkyl wherein substituted naphthyl is as defined above, amino, alkylamino, dialkylamino, (hydroxyalkyl)(alkyl)amino, (dihydroxyalkyl)(alkyl)amino, aminoalkyl, alkoxycarbonylalkyl, carboxyalkyl, (N-protected)-aminoalkyl, alkylaminoalkyl, (N-protected)(alkyl)aminoalkyl, dialkylaminoalkyl, (heterocyclic)alkyl, a substituted or unsubstituted heterocyclic as defined above, aminocycloalkyl, aminoalkylamino, (dialkylaminoalkyl)(alkyl)amino, phenylalkylamino, (substituted phenyl)alkylamino wherein substituted phenyl is as defined above, naphthylalkylamino, (substituted naphthyl)alkylamino wherein substituted naphthyl is as defined above, (phenylalkyl)(alkyl)amino, ((substituted phenyl)alkyl)(alkyl)amino wherein substituted phenyl is as defined above, (naphthylalkyl)(alkyl)amino, ((substituted naphthyl)alkyl)(alkyl)amino wherein substituted naphthyl is as defined above, alkoxyalkyl(alkyl)amino, (polyalkoxy)alkyl(alkyl)amino,

di-(alkoxyalkyl)amino, di-(hydroxyalkyl)amino, di-((polyalkoxy)alkyl)amino, ((heterocyclic)alkyl)(alkyl)amino, ((heterocyclic)alkyl)amino, (heterocyclic)(alkyl)amino, (alkylaminoalkyl)(alkyl)amino, (dialkylaminoalkyl)(alkyl)amino, ((alkoxy)(alkyl)aminoalkyl)(alkyl)amino, ((alkoxy)aminoalkyl)(alkyl)amino, polyalkoxy or (polyalkoxy)alkyl; or A_g is $R_{41g}CH(OH)CH_2-$ or $R_{41g}CH(OH)CH(OH)-$ wherein R_{41g} is loweralkyl, cycloalkyl, phenyl, substituted phenyl as defined above, naphthyl, substituted naphthyl as defined above, phenylalkyl, (substituted phenyl)alkyl wherein substituted phenyl is as defined above, naphthylalkyl, (substituted naphthyl)alkyl wherein substituted naphthyl is as defined above, phenylalkoxyalkyl, (substituted phenyl)alkoxyalkyl wherein substituted phenyl is as defined above, naphthylalkoxyalkyl, (substituted naphthyl)alkoxyalkyl wherein substituted naphthyl is as defined above, thioalkoxyalkyl, loweralkylsulfinylalkyl, loweralkylsulfonylalkyl, phenylthioalkyl, (substituted phenyl)thioalkyl wherein substituted phenyl is as defined above, naphthylthioalkyl, (substituted naphthyl)thioalkyl wherein substituted naphthyl is as defined above, phenylsulfonylalkyl, (substituted phenyl)sulfonylalkyl wherein substituted phenyl is as defined above, naphthylsulfonylalkyl, (substituted naphthyl)sulfonylalkyl wherein substituted naphthyl is as defined above, aminoalkyl, alkoxycarbonylalkyl, carboxyalkyl, (N-protected)aminoalkyl, alkylaminoalkyl, (N-protected)(alkyl)aminoalkyl, dialkylaminoalkyl, heterocyclicalkyl, a substituted or unsubstituted

heterocyclic as defined above, aminocycloalkyl or (polyalkoxy)alkyl;

W_g is C=O, CHOH or NR_{2g} wherein R_{2g} is hydrogen or loweralkyl;

U_g is C=O, CH_2 or NR_{2g} wherein R_{2g} is hydrogen or loweralkyl, with the proviso that when W_g is CHOH then U_g is CH_2 and with the proviso that U_g is C=O or CH_2 when W_g is NR_{2g};

V_g is CH, C(OH) or C(halogen) with the proviso that V_g is CH when U_g is NR_{2g};

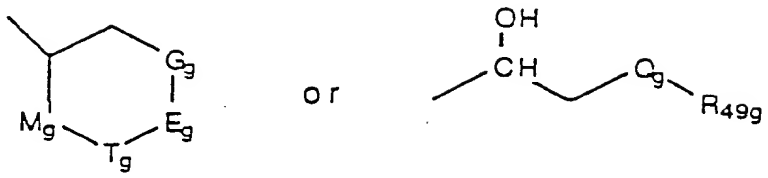
R_{1g} is loweralkyl, cycloalkylalkyl, benzyl, (alpha, alpha)-dimethylbenzyl, 4-methoxybenzyl, halobenzyl, 4-hydroxybenzyl, (1-naphthyl)methyl, (2-naphthyl)methyl, (unsubstituted heterocyclic)methyl, (substituted heterocyclic)methyl wherein unsubstituted or substituted heterocyclic is as defined above, phenethyl, 1-benzyloxyethyl, phenoxy, thiophenoxy or anilino, provided that B_g is CH_2 or CHOH or A_g is hydrogen when R_{1g} is phenoxy, thiophenoxy or anilino;

R_{3g} is loweralkyl, loweralkenyl, ((alkoxy)alkoxy)alkyl, carboxyalkyl, (thioalkoxy)alkyl, azidoalkyl, aminoalkyl, (alkyl)aminoalkyl, dialkylaminoalkyl, (alkoxy)(alkyl)aminoalkyl, (alkoxy)aminoalkyl, benzyl or heterocyclic ring substituted methyl;

R_{4g} is loweralkyl, cycloalkylmethyl or benzyl;

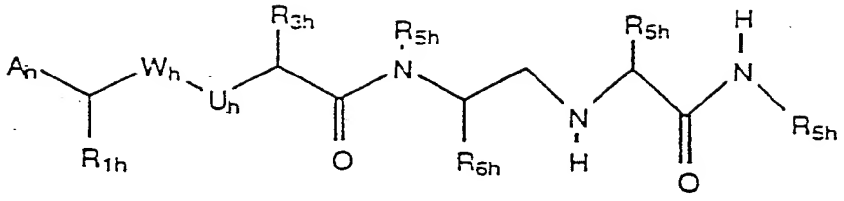
R_{5g} is OH or NH_2; and

Z_g is

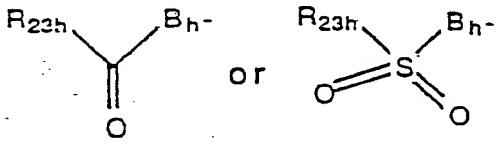


wherein M_g is O, S or NH, T_g is C=O, C=S, S, S(O), $S(O)_2$ or CH_2, E_g is O, S, NR_{6g} wherein R_{6g} is hydrogen, loweralkyl, hydroxyalkyl, hydroxy, alkoxy, amino, or alkylamino, or E_g is $CR_{6g}R_{42g}$ wherein R_{6g} is as defined above and R_{42g} is hydrogen or loweralkyl or E_g is $C=CR_{43g}R_{44g}$ wherein R_{43g} and R_{44g} are independently selected from hydrogen and loweralkyl, G_g is absent, CH_2, or NR_{11g} wherein R_{11g} is hydrogen or loweralkyl, with the proviso that when G_g is NR_{11g} then R_{6g} is loweralkyl or hydroxyalkyl, Q_g is $CR_{45g}R_{46g}$ wherein R_{45g} and R_{46g} are independently selected from hydrogen and loweralkyl or Q_g is $C=CR_{47g}R_{48g}$ wherein R_{47g} and R_{48g} are independently selected from hydrogen and loweralkyl, and R_{49g} is $-CH_2OH$, carboxy, alkoxycarbonyl or $-CONR_{50g}R_{51g}$ wherein R_{50g} is hydrogen or loweralkyl and R_{51g} is hydrogen, loweralkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl or alkoxyalkyl;

(8).



wherein A_h is hydrogen, loweralkyl, arylalkyl, $-OR_{20h}$ or $-SR_{20h}$ wherein R_{20h} is hydrogen, loweralkyl or aminoalkyl, $-NR_{21h}R_{22h}$ wherein R_{21h} and R_{22h} are independently selected from hydrogen, loweralkyl, aminoalkyl, cyanoalkyl and hydroxyalkyl; or A_h is



wherein B_h is NH, alkylamino, S, O, CH_2, $NHCH_2$ or CHOH; and R_{23h} is loweralkyl, cycloalkyl, aryl, arylalkyl, alkoxy, alkenyloxy, hydroxyalkoxy, dihydroxyalkoxy, arylalkoxy, arylalkoxyalkyl, amino, alkylamino, dialkylamino, (hydroxyalkyl)(alkyl)amino, ((dialkylamino)alkyl)(alkyl)amino, (dihydroxyalkyl)(alkyl)amino, aminoalkyl, N-protected aminoalkyl, alkylaminoalkyl, (N-protected)(alkyl)aminoalkyl, dialkylaminoalkyl, (heterocyclic)alkyl, or a substituted or unsubstituted heterocyclic;

W_h is C=O or CHOH;

U_h is CH_2 or NR_{2h}, wherein R_{2h} is hydrogen or loweralkyl, provided that when W_h is CHOH

then U_h is CH_2;

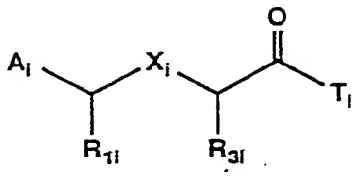
R_{1h} is loweralkyl, cycloalkylalkyl, benzyl, 4-methoxybenzyl, 4-hydroxybenzyl, halobenzyl, (1-naphthyl)methyl, (2-naphthyl)methyl, (4-imidazolyl)methyl, (alpha,alpha)-dimethylbenzyl, 1-benzyloxyethyl, phenethyl, phenoxy, thiophenoxy or anilino, provided that when R_{1h} is phenoxy, thiophenoxy or anilino, then B_h is CH_2 or CHOH or A_h is hydrogen;

R_{3h} is loweralkyl, loweralkenyl, ((alkoxy)alkoxy)alkyl, carboxyalkyl, (thioalkoxy)alkyl, benzyl or heterocyclic ring substituted methyl;

R_{5h} is hydrogen or loweralkyl;

R_{6h} is loweralkyl, cycloalkylmethyl, or benzyl;

(9).



wherein A_i is

(I) $R_{5i}C(O)-(CH_2)_{w"}-$ wherein

1) w" is 0 to 4 and

2) R_{5i} is

i) hydroxy,

ii) alkoxy,

iii) thioalkoxy,

iv) amino or

v) substituted amino;

(II) alkylsulfonyl, (aryl)sulfonyl or (heterocyclic)sulfonyl;

(III) aryl, arylalkyl, heterocyclic or (heterocyclic)alkyl; or

(IV) $R_{90i}-$ or $R_{90i}NHC(O)-$ wherein R_{90i} is a C_1 to C_4 straight or branched carbon chain substituted by a substituent selected from

1) carboxy,

2) alkoxycarbonyl,

3) alkylsulfonyl,

4) aryl,

5) arylsulfonyl,

6) heterocyclic or

7) (heterocyclic)sulfonyl);

R_{1i} is

(I) hydrogen,

(II) loweralkyl,
(III) loweralkenyl,
(IV) cycloalkylalkyl,
(V) cycloalkenylalkyl,
(VI) aryloxyalkyl,
(VII) thioaryloxyalkyl,
(VIIII) arylalkoxyalkyl,
(IX) arylthioalkoxyalkyl or
(X) a C_1 to C_3 straight or branched carbon chain substituted by a substituent selected from
1) alkoxy,
2) thioalkoxy,
3) aryl and
6) heterocyclic;

X_i is
(I) CH_2,
(II) CHOH,
(III) C(O),
(IV) NH,
(V) O,
(VI) S,
(VII) S(O),
(VIII) SO_2,
(IX) N(O) or
(X) -P(O)O-;

R_{3i} is
(I) loweralkyl,
(II) haloalkyl,
(III) loweralkenyl,
(IV) cycloalkylalkyl,

(V) cycloalkenylalkyl,

(VI) alkoxyalkyl,

(VII) thioalkoxyalkyl,

(VIII) (alkoxyalkoxy)alkyl,

(IX) hydroxyalkyl,

(X) $-(CH_2)_{ee}NHR_{12i}$

wherein

1) ee is 1 to 3 and

2) R_{12i} is

i) hydrogen,

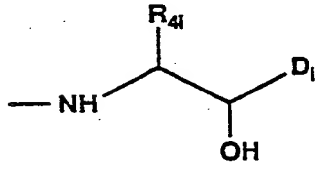
ii) loweralkyl or

iii) an N-protecting group;

(XI) arylalkyl or

(XII) (heterocyclic)alkyl; and

T_i is



wherein R_{4i} is

(I) loweralkyl,

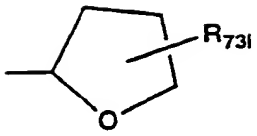
(II) cycloalkylalkyl

(III) cycloalkenylalkyl or

(III) arylalkyl; and

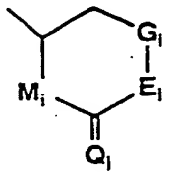
D_i is

(I)



wherein R_{73i} is loweralkyl,

(II)



wherein

1) M_i is
   i) O,
   ii) S or
   iii) NH;
2) Q_i is
   i) O or
   ii) S;
3) Ei is
   i) O,
   ii) S,
   iii) CHR_{73i} wherein R_{73i} is loweralkyl,
   iv) $C=CH_2$ or
   v) NR_{18i} wherein R_{18i} is
      a) hydrogen,
      b) loweralkyl,
      c) hydroxyalkyl,
      d) hydroxy,
      e) alkoxy,

f) amino or

g) alkylamino;

and

4) G_i is

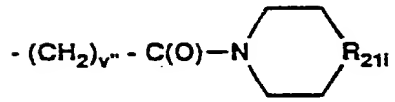
i) absent,

ii) CH_2 or

iii) NR_{19i} wherein R_{19i} is hydrogen or loweralkyl,

with the proviso that when G_i is NR_{19i}, then R_{18i} is loweralkyl or hydroxyalkyl;

(III)



wherein

1) v" is 0 or 1 and

2) R_{21i} is

i) NH,

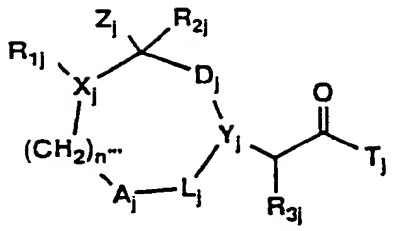
ii) O,

iii) S or

iv) SO_2; or

(IV) a substituted methylene group; and

(10).



wherein X_j is

(I) N,

(II) O or

(III) CH;

R_{1j} is

(I) absent,

(II) hydrogen,

(III) an N-protecting group,

(IV) aryl,

(V) heterocyclic, or

(VI) R_{6j}-Q_j- wherein

1) R_{6j} is

i) loweralkyl,

ii) amino,

iii) alkylamino,

iv) dialkylamino,

v) (alkoxyalkyl)(alkyl)amino,

vi) (alkoxyalkoxyalkyl)(alkyl)amino,

vii) aryl,

viii) arylalkyl,

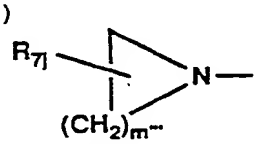
ix) aminoalkyl,

x) (N-protected)aminoalkyl,

xi) alkoxy,

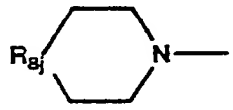
xii) substituted loweralkyl wherein the substituent is selected from alkoxy, thioalkoxy, halogen, alkylamino, (N-protected)(alkyl)amino and dialkylamino,

xiii)



wherein m''' is 1 to 5 and R_{7j} is hydrogen, hydroxy, alkoxy, thioalkoxy, alkoxyalkoxy, polyalkoxy, amino, (N-protected)amino, alkylamino, (N-protected)(alkyl)amino or dialkylamino; or

xiv)



wherein R_{8j} is O, S, SO_2, O=C or $R_{9j}N$ wherein R_{9j} is hydrogen, loweralkyl or an N-protecting group; and

2) Q_j is

i) C=O or

ii) CH_2,

with the proviso that X_j is N when R_{1j} is an N-protecting group;

(VII) $R_{54j}S(O)_2-$ wherein R_{54j} is

1) amino,

2) alkylamino,

3) dialkylamino,

4) loweralkyl,
5) haloalkyl,
6) aryl,
7) p-biphenyl,
8) heterocyclic or

(VIII) $(R_{55j})_2P(O)-$ wherein R_{55j} is
1) alkoxy,
2) alkylamino or
3) dialkylamino;

A_j and L_j are independently selected from
(I) absent,
(II) C=O,
(III) SO_2 and
(IV) CH_2;

D_j is
(I) C=O,
(II) SO_2 or
(III) CH_2;

Y_j is
(I) N or
(II) CH;

R_{2j} is
(I) hydrogen,
(II) loweralkyl,
(III) cycloalkylalkyl,
(IV) $-CH_2-R_{10j}-(CH_2)_{q'''}-R_{11j}$ wherein
1) q''' is 0, 1 or 2,

2) R_{10j} is absent or R_{10j} is O, NH or S only when q''' is 1 or 2, and

3) R_{11j} is

i) aryl or

ii) heterocyclic;

Z_j is

(I) hydrogen or

(II) $-R_{28j}C(O)R_{29j}$, $-R_{28j}S(O)_2R_{29j}$ or $-R_{28j}C(S)R_{29j}$ wherein

1) R_{28j} is

i) NH,

ii) $-N(R_{200j})-$ wherein R_{200j} is loweralkyl or benzyl or

iii) CH_2 and

2) R_{29j} is

i) alkoxy,

ii) benzyloxy,

iii) alkylamino,

iv) dialkylamino,

v) aryl or

vi) heterocyclic;

R_{3j} is

(I) hydrogen,

(II) loweralkyl,

(III) loweralkenyl,

(IV) cycloalkylalkyl,

(V) cycloalkenylalkyl,

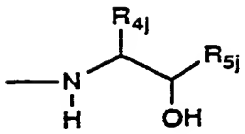
(VI) alkoxyalkyl,

(VII) thioalkoxyalkyl,

(VIIII) (alkoxyalkoxy)alkyl,
(IX) (polyalkoxy)alkyl,
(X) arylalkyl or
(XI) (heterocyclic)alkyl;

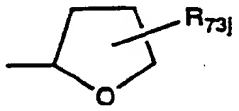
n''' is 0 or 1; and

T_j



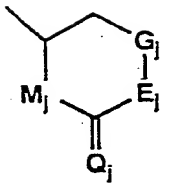
wherein R_{4j} is
(I) loweralkyl,
(II) cycloalkylalkyl or
(III) arylalkyl; and

R_{5j} is
(I)



wherein R_{73j} is loweralkyl,

(II)



wherein

1) M_j is
   i) O,
   ii) S or
   iii) NH;
2) Q_j is
   i) O or
   ii) S;
3) E_j is
   i) O,
   ii) S,
   iii) CHR_{61j} wherein R_{61j} is loweralkyl,
   iv) $C=CH_2$ or
   v) NR_{18j} wherein R_{18j} is
      a) hydrogen,
      b) loweralkyl,
      c) hydroxyalkyl,
      d) hydroxy,
      e) alkoxy,
      f) amino or
      g) alkylamino;

and

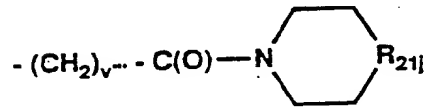
4) G_j is
   i) absent,

ii) CH_2 or

iii) NR_{19j} wherein R_{19j} is hydrogen or loweralkyl,

with the proviso that when G_j is NR_{19j}, then R_{18j} is loweralkyl or hydroxyalkyl;

(III)



wherein

1) v''' is 0 or 1 and

2) R_{21j} is

i) NH,

ii) O,

iii) S or

iv) SO_2; or

(IV) a substituted methylene group;

or a pharmaceutically acceptable salt, ester or prodrug thereof.

The term "loweralkyl" as used herein refers to straight or branched chain alkyl radicals containing from 1 to 7 carbon atoms including but not limited to methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methyl-pentyl, 2,2-dimethylbutyl, n-heptyl, 2-methylhexyl and the like.

the term "loweralkenyl" as used herein refers to a straight or branched chain loweralky radical which contains at least one carbon-carbon double bond.

The term "cycloalkyl" as used herein refers to an aliphatic ring having 3 to 7 carbon atoms.

The term "cycloalkylalkyl" as used herein refers to a cycloalkyl residue appended to a loweralkyl radical and includes but is not limited to cyclohexylmethyl and cyclopentylmethyl.

The term "cycloalkenyl" as used herein refers to an aliphatic ring having 3-7 carbon atoms and also having at least one carbon-carbon double bond including, but not limited to, cyclohexenyl and the like.

The term "cycloalkenylalkyl" as used herein refers to a cycloalkenyl group appended to a loweralkyl radical including, but not limited to, cyclohexenylmethyl, cylcopentenylethyl and the like.

The term "arylalkyl" as used herein refers to an aryl group as defined herein appended to a loweralkyl radical including but not limited to benzyl, 1- and 2-naphthylmethyl, halobenzyl, and alkoxybenzyl.

The term "phenylalkyl" as used herein refers to a phenyl group appended to a loweralkyl radical, including, but not limited to benzyl, phenethyl and the like.

The term "(substituted phenyl)alkyl" as used herein refers to a substituted phenyl group appended to a loweralkyl radical wherein the phenyl ring is substituted with one, two or three substituents chosen from the group loweralkoxy, loweralkyl, amino, loweralkylamino, hydroxy, halo, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxy, carboalkoxy and carboxamide, including, but not limited to halobenzyl, alkoxybenzyl and the like.

The term "naphthylalkyl" as used herein refers to a naphthyl group appended to a loweralkyl radical, including, but not limited to 1-naphthylmethyl, 2-naphthylmethyl and the like.

The term "(substituted naphthyl)alkyl" as used herein refers to a substituted naphthyl group appended to a loweralkyl radical wherein the naphthyl ring is substituted with one, two or three substituents chosen from the group loweralkoxy, loweralkyl, amino, loweralkylamino, hydroxy, halo, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxy, carboalkoxy and carboxamide, including, but not limited to halonaphthylmethyl, alkoxynaphthylmethyl and the like.

The term "(heterocyclic)alkyl" as used herein refers to an unsubstituted or substituted heterocyclic ring as defined below appended to a loweralkyl radical, including, but not limited to imidazolylmethyl, thiazolylmethyl and the like.

The term "hydroxyalkyl" as used herein refers to -OH appended to a loweralkyl radical.

The term "alkoxyalkyl" as used herein refers to an alkoxy group appended to a loweralkyl radical.

The term "arylalkoxyalkyl" as used herein refers to an arylalkoxy appended to a loweralkyl radical.

The term "phenylalkoxyalkyl" as used herein refers to a phenylalkoxy group appended to a loweralkyl radical, including, but not limited to phenylmethoxymethyl and the like.

The term "(substituted phenyl)alkoxyalkyl" as used herein refers to a (substituted phenyl)alkoxy group appended to a loweralkyl radical, including, but not limited to 4-chlorophenylmethoxymethyl.

The term "naphthylalkoxyalkyl" as used herein refers to a naphthylalkoxy group appended to a loweralkyl radical, including, but not limited to 1-naphthylmethoxymethyl and the like.

The term "(substituted naphthyl)alkoxyalkyl" as used herein refers to a (substituted naphthyl)alkoxy group appended to a loweralky radical, including, but not limited to halonaphthylmethoxymethyl and the like.

The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group appended to a loweralkyl radical.

The term "((alkoxy)alkoxy)alkyl" as used herein refers to an alkoxy group appended to an alkoxy group which is appended to a loweralkyl radical, including, but not limited to methoxymethoxymethyl and the like.

The term "polyalkoxyalkyl" as used herein refers to a polyalkoxy residue appended to a loweralkyl radical, including, but not limited to methoxyethoxymethoxymethyl and the like.

The term "aminoalkyl" as used herein refers to $-NH_2$ appended to a loweralkyl radical.

The term "alkylaminoalkyl" as used herein refers to $-NHR_{70}$ appended to a loweralkyl radical, wherein R_{70} is a loweralkyl radical.

The term "dialkylaminoalkyl" as used herein refers to a dialkylamino appended to a loweralkyl radical.

The term "aminocycloalkyl" as used herein refers to an $-NH_2$ appended to a cycloalkyl radical.

The term "N-protected aminoalkyl" as used herein refers to $-NHR_{71}$ appended to a loweralkyl group, wherein R_{71} is an N-protecting group.

The term "(N-protected)(alkyl)amino alkyl" as used herein refers to $NR_{71}R_{72}$ which is appended to a loweralkyl radical, wherein R_{71} is defined as above and R_{72} is a loweralkyl group.

The term "alkoxycarbonylalkyl" as used herein refers to $R_{73}COR_{74}-$, wherein R_{73} is an alkoxy group and R_{74} is a loweralkyl radical.

The term "carboxyalkyl" as used herein refers to a carboxylic acid group (-COOH) appended to a loweralkyl radical.

The term "cyanoalkyl" as used herein refers to -CN appended to a loweralkyl radical.

The term "azidoalkyl" as used herein refers to $-N_3$ appended to a loweralkyl radical.

The term "(alkoxy)aminoalkyl" as used herein refers to an alkoxy group appended to an amino group which in turn is appended to a loweralkyl radical.

The term "(alkoxy)(alkyl)aminoalkyl" as used herein refers to an $-NR_{75}R_{76}$ group appended to a loweralkyl radical wherein R_{75} is an alkoxy group and R_{76} is a loweralkyl group.

The term "loweralkylsulfinylalkyl" as used herein refers to a $R_{77}S(O)-$ group appended to a loweralkyl radical wherein R_{77} is a loweralkyl group.

The term "loweralkylsulfonylalkyl" as used herein refers to a $R_{78}S(O)_2-$ group appended to a loweralkyl radical wherein R_{78} is a loweralkyl group.

The term "phenylthioalkyl" as used herein refers to a $R_{79}S-$ group appended to a loweralkyl radical wherein R_{79} is a phenyl group.

The term "(substituted phenyl)thioalkyl" as used herein refers to a $R_{80}S-$ group appended to a loweralkyl radical wherein R_{80} is a substituted phenyl group.

The term "naphthyl thioalkyl" as used herein refers to a $R_{81}S-$ group appended to a loweralkyl radical wherein R_{81} is a naphthyl group.

The term "(substituted naphthyl)thioalkyl" as used herein refers to a $R_{82}S-$ group appended to a loweralkyl radical wherein R_{82} is a substituted naphthyl group.

The term "phenylsulfonylalkyl" as used herein refers to a $R_{83}S(O)_2-$ group appended to a loweralkyl radical wherein R_{83} is a phenyl group.

The term "(substituted phenyl)sulfonylalkyl" as used herein refers to a $R_{84}S(O)_2-$ group appended to a loweralkyl radical wherein R_{84} is a substituted phenyl group.

The term "naphthylsulfonylalkyl" as used herein refers to a $R_{85}S(O)_2-$ group appended to a loweralkyl group wherein R_{85} is a naphthyl group.

The term "(substituted naphthyl)sulfonylalkyl" as used herein refers to a $R_{86}S(O)_2-$ group appended to a loweralkyl group wherein R_{86} is a substituted naphthyl group.

The term "carboxyalkoxyalkyl" as used herein refers to a carboxylic acid group (-COOH) appended to an alkoxy group which is appended to a loweralkyl radical.

The term "alkoxycarbonylalkoxyalkyl" as used herein refers to an alkoxycarbonyl group ($R_{87}CO-$ wherein R_{87} is an alkoxy group) appended to an alkoxy group which is appended to a loweralkyl radical.

The term "(amino)carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxylic acid group (-COOH) and an amino group ($-NH_2$).

The term "((N-protected)amino)carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxylic acid group (-COOH) and $-NHR_{88}$ wherein R_{88} is an N-protecting group.

The term "(alkylamino)carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxylic acid group (-COOH) and an alkylamino group.

The term "((N-protected)alkylamino)-carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxylic acid group (-COOH) and an $-NR_{89}R_{90}$ wherein R_{89} is as defined above and R_{90} is a loweralkyl group.

The term "(dialkylamino)carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxylic acid group (-COOH) and $-NR_{91}R_{92}$ wherein R_{91} and R_{92} are independently selected from loweralkyl.

The term "(amino)alkoxycarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkoxycarbonyl group as defined above and an amino group ($-NH_2$).

The term "((N-protected)amino)alkoxy-carbonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkoxycarbonyl group as

defined above and $-NHR_{93}$ wherein R_{93} is as defined above.

The term "(alkylamino)alkoxycarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkoxycarbonyl group as defined above and an alkylamino group as defined above.

The term "((N-protected)alkylamino)-alkoxycarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkoxycarbonyl group as defined above and $-NR_{94}R_{95}$ wherein R_{94} is an N-protecting group and R_{95} is a loweralkyl group.

The term "(dialkylamino)alkoxycarbonyalkyl" as used herein refers to a loweralkyl radical to which is appended an alkoxycarbonyl group as defined above and $-NR_{96}R_{97}$ wherein R_{96} and R_{97} are independently selected from loweralkyl.

The term "carboxyalkylamino" as used herein refers to $-NHR_{98}$ wherein R_{98} is a carboxyalkyl group.

The term "alkoxycarbonylalkylamino" as used herein refers to $-NHR_{99}$ wherein R_{99} is an alkoxycarbonylakyl group.

The term "(amino)carboxyalkylamino" as used herein refers to $-NHR_{100}$ wherein R_{100} is an (amino)carboxyalkyl group.

The term "((N-protected)amino)carboxy-alkylamino" as used herein refers to $-NHR_{101}$ wherein R_{101} is an ((N-protected)amino)carboxyalkyl group.

The term"(alkylamino)carboxyalkylamino" as used herein refers to $-NHR_{102}$ wherein R_{102} is an (alkylamino)carboxyalkyl group.

The term "((N-protected)alkylamino)-carboxyalkylamino" as used herein refers to $-NHR_{103}$

wherein R_{103} is an ((N-protected)alkylamino)-carboxyalkyl group.

The term "(dialkylamino)carboxyalkylamino" as used herein refers to $-NHR_{104}$ wherein R_{104} is a (dialkylamino)carboxyalkyl group.

The term"(amino)alkoxycarbonylalkylamino" as used herein refers to $-NHR_{105}$ wherein R_{105} is an (amino)alkoxycarbonylalkyl group.

The term "((N-protected)amino)alkoxy-carbonylalkylamino" as used herein refers to $-NHR_{106}$ wherein R_{106} is an ((N-protected)amino)-alkoxycarbonylalkyl group.

The term "(alkylamino)alkoxycarbonylalkylamino" as used herein refers to $-NHR_{107}$ wherein R_{107} is an (alkylamino)alkoxycarbonylalkyl group.

The term "((N-protected)alkylamino)alkoxy-carbonylalkylamino" as used herein refers to $-NHR_{108}$ wherein R_{108} is an ((N-protected)alkylamino)-alkoxycarbonylalkyl group.

The term "(dialkylamino)alkoxycarbonyl-alkylamino" as used herein refers to $-NHR_{109}$ wherein R_{109} is a (dialkylamino)alkoxycarbonylalkyl group.

The term "alkylidene" as used herein refers to a straight or branched chain alkyl radical which is attached via a carbon-carbon double bond and includes but is not limited to methylidene, ethylidene, 1-propylidene, 1-butylidene, 1-pentylidene, 2-propylidene, 2-butylidene, 2-pentylidene, 3-pentylidene, 3-hexylidene, 3-heptylidene and 4-heptylidene.

The term "alkylidene oxide" as used herein refers to an epoxide moiety which is derived from an alkylidene group.

The term "amino" as used herein refers to an $-NH_2$ substituent.

The term "alkylamino" as used herein refers to $-NHR_{110}$, wherein R_{110} is a loweralkyl group.

The term "dialkylamino" as used herein refers to $-NR_{111}R_{112}$, wherein R_{111} and R_{112} are independently selected from loweralkyl groups.

The term "arylalkylamino" as used herein refers to $R_{113}NH-$, wherein R_{113} is an arylalkyl residue.

The term "arylalkyl(alkyl)amino" as used herein refers to $R_{114}R_{115}N-$, wherein R_{114} is an arylalkyl residue and R_{115} is a loweralkyl residue.

The term "phenylalkylamino" as used herein refers to a phenylalkyl group appended to an amino radical, including, but not limited to benzylamino and the like.

The term "(substituted phenyl)alkylamino" as used herein refers to a (substituted phenyl)alkyl group appended to an amino radical, including, but not limited to 4-chlorobenzylamino and the like.

The term "napthylalkylamino" as used herein refers to a naphthylalkyl group appended to an amino radical, including, but not limited to 1-naphthylmethylamino and the like.

The term "(substituted naphthyl)alkylamino" as used herein refers to a (substituted naphthyl)alkyl group appended to an amino radical.

The term "(phenylalkyl)(alkyl)amino" as used herein refers to $R_{116}R_{117}N-$, wherein R_{116} is a phenylalkyl residue and R_{117} is a loweralkyl residue.

The term "((substituted phenyl)alkyl)-(alkyl)amino" as used herein refers to $R_{118}R_{119}N-$ wherein R_{118} is a (substituted phenyl)alkyl group and R_{119} is a loweralkyl group.

The term "(naphthylalkyl)(alkyl)amino" as used herein refers to $R_{120}R_{121}N-$ wherein R_{120} is a naphthylalkyl group and R_{121} is a loweralkyl group.

The term "((substituted naphthyl)alkyl)-(alkyl)amino" as used herein refers to $R_{122}R_{123}N-$ wherein R_{122} is a (substituted naphthyl)alkyl group and R_{123} is a loweralkyl group.

The term "aminoalkylamino" as used herein refers to $R_{124}NH-$ where R_{124} is an aminoalkyl residue.

The term "dialkylamino(alkyl)amino" as used herein refers to $R_{125}R_{126}N-$, wherein R_{125} is a dialkylamino residue appended to a loweralkyl residue and R_{126} is a loweralkyl residue.

The term "((dialkylamino)alkyl)(alkyl)amino" as used herein refers to $-NR_{127}R_{128}$ wherein R_{127} is a dialkylamino residue appended to a loweralkyl residue and R_{128} is a loweralkyl residue.

The term "(hydroxyalkyl)(alkyl)amino" as used herein refers to $-NR_{129}R_{130}$ wherein R_{129} is a hydroxyalkyl group and R_{130} is a loweralkyl group.

The term "(di-hydroxyalkyl)(alkyl)amino" as used herein refers to a loweralkyl group which is disubstituted with -OH radicals appended to an amino group, which amino group also has appended another loweralkyl group.

The term "di-(hydroxyalkyl)amino" as used herein refers to $R_{131}R_{132}N-$, wherein R_{131} and R_{132} are hydroxyalkyl residues.

The term "alkoxyalkyl(alkyl)amino" as used herein refers to $R_{133}R_{134}N-$, wherein R_{133} is a loweralkyl group and R_{134} is an alkoxyalkyl group.

The term "di-(alkoxyalkyl)amino" as used herein refers to $R_{135}R_{136}N-$, wherein R_{135} and R_{136} are alkoxy residues appended to loweralkyl residues.

The term "di-(polyalkoxyalkyl)amino" as used herein refers to $R_{137}R_{138}N-$, wherein R_{137} and R_{138} are polyalkoxy residues appended to loweralkyl residues.

The term "((polyalkoxy)alkyl)(alkyl)amino" as used herein refers to $R_{139}R_{140}N-$, wherein R_{139} is a polyalkoxy residue appended to a loweralkyl radical and R_{140} is a loweralkyl residue.

The term "((heterocyclic)alkyl)(alkyl)amino" as used herein refers to $-NR_{141}R_{142}$ wherein R_{141} is a heterocyclicalkyl group and R_{142} is a loweralkyl group.

The term "(heterocyclicalkyl)amino" as used herein refers to $-NHR_{143}$ wherein R_{143} is a heterocyclic alkyl group.

The term "(heterocyclic)(alkyl)amino" as used herein refers to $-NR_{144}R_{145}$ wherein R_{144} is a substituted or unsubstituted heterocyclic group and R_{145} is a loweralkyl group.

The term "(alkylaminoalkyl)(alkyl)amino" as used herein refers to $-NR_{146}R_{147}$ wherein R_{146} is an alkylaminoalkyl group and R_{147} is a loweralkyl group.

The term "(dialkylaminoalkyl)(alkyl)amino" as used herein refers to $-NR_{148}R_{149}$ wherein R_{148} is a dialkylaminoalkyl group and R_{149} is a loweralkyl group.

The term "((alkoxy)(alkyl)aminoalkyl)-(alkyl)amino" as used herein refers to $-NR_{150}R_{151}$ wherein R_{150} is $-NR_{152}R_{153}$ appended to a loweralkyl radical wherein R_{152} is an alkoxy group and R_{153} is a loweralkyl group and R_{151} is a loweralkyl group.

The term "((alkoxy)aminoalkyl)(alkyl)amino" as used herein refers to $-NR_{154}R_{155}$ wherein R_{154} is $-NHR_{156}$ appended to a loweralkyl group and wherein R_{156} is an alkoxy group and R_{155} is a loweralkyl group.

The term "(alkoxyalkoxyalkyl)(alkyl)amino" as used herein refers to $-NR_{305}R_{306}$ wherein R_{305} is an alkoxyalkoxyalkyl group and R_{306} is a loweralkyl group.

The term "di(alkoxyalkoxyalkyl)amino" as used herein refers to $-NR_{307}R_{308}$ wherein R_{307} and R_{308} are alkoxyalkoxyalkyl groups.

The term "alkylsulfonylamino" as used herein refers to $R_{309}NH-$ wherein R_{309} is an alkylsulfonyl gorup.

The term "arylsulfonylamino" as used herein refers to $R_{310}NH-$ wherein R_{310} is an arylsulfonyl group.

The term "alkylaminocarbonylamino" as used herein refers to $R_{311}C(O)NH-$ wherein R_{311} is an alkylamino group.

The term "alkylaminocarbonyloxy" as used herein refers to $R_{312}C(O)O-$ wherein R_{312} is an alkylamino group.

The term "alkoxycarbonyloxy" as used herein refers to $R_{313}C(O)O-$ wherein R_{313} is an alkoxy group.

The term "loweralkylcarbonyl" as used herein refers to $R_{157}C(O)-$ wherein R_{157} is a loweralkyl group, including, but not limited to acetyl, propionyl and the like.

The terms "alkoxy" and "thioalkoxy" as used herein refer to $R_{158}O-$ and $R_{158}S-$, respectively, wherein R_{158} is a loweralkyl group.

The term "alkoxyalkoxy" as used herein refers to an alkoxy group appended to an alkoxy radical including, but not limited to, methoxymethoxy and the like.

The term "aryloxyalkyl" as used herein refers to an aryloxy group ($R_{303}O-$ wherein R_{303} is an aryl group) appended to a loweralkyl radical.

The term "thioaryloxyalkyl" as used herein refers to a thioaryloxy group ($R_{304}S-$ wherein R_{304} is an aryl group) appended to a loweralkyl radical.

The terms "arylalkoxy" and "arylthioalkoxy" as used herein refer to an aryl group appended to an alkoxy radical or a thioalkoxy radical, respectively, including, but not limited to, phenoxymethyl, thiophenoxymethyl and the like.

The terms "arylalkoxyalkyl" and "arylthioalkoxyalkyl" as used herein refer to an arylalkoxy group or an arylthioalkoxy group, respectively, appended to a loweralkyl radical.

The term "alkenyloxy" as used herein refers to $R_{159}O-$, wherein R_{159} is an alkyl group of 1 to 7 carbon atoms which contains at least one carbon-carbon double bond.

The term "hydroxyalkoxy" as used herein refers to -OH appended to an alkoxy radical.

The term "dihydroxyalkoxy" as used herein refers to an alkoxy radical which is disubstituted with -OH radicals.

The term "arylalkoxy" as used herein refers to an aryl group appended to an alkoxy radical.

The term "alkylaryloxy" as used herein refers to $R_{160}O-$ wherein R_{160} is an alkylaryl group.

The term "phenylalkoxy" as used herein refers to a phenyl group appended to an alkoxy radical, including, but not limited to benzyloxy and the like.

The term "(substituted phenyl)alkoxy" as used herein refers to a substituted phenyl group appended to an alkoxy radical, including, but not limited to 4-chlorobenzyloxy and the like.

The term "naphthylalkoxy" as used herein refers to a naphthyl group appended to an alkoxy radical.

The term "(substituted naphthyl)alkoxy" as used herein refers to a substituted naphthyl group appended to an alkoxy radical.

The term "polyalkoxy" as used herein refers to $R_{161}O-$, wherein R_{161} is a straight or branched chain containing 1-5, $C_m-O-C_{m'}$ linkages where m and m' are independently 1 to 3.

The terms "halo" or "halogen" as used herein refer to Cl, Br, F or I substituents.

The term "haloalkyl" as used herein refers to a loweralkyl radical in which one or more hydrogen atomsare replaced by halogen including, but not limited to fluoromethyl, 2-chloroethyl, trifluoromethyl, 2,2-dichloroethyl and the like.

The term "polyhaloalkyl" as used herein refers to a loweralkyl radical substituted with two or more halogens, including, but not limited to trifluoromethyl, 2,2-dichloroethyl and the like.

The term "halobenzyl" as used herein refers to a halo substituent appended to the phenyl ring of a benzyl radical.

The term "halophenyl" as used herein refers to a halo substituent appended to a phenyl radical.

The term "alkylsulfonyl" as use dherein refers to $R_{300}S(O)_2-$ wherein R_{300} is a loweralkyl group.

The term " (aryl)sulfonyl" as used herein refers to $R_{301}S(O)_2$- werein R_{301} is an aryl group.

The term "(heterocyclic)sulfonyl" as used herein refers to $R_{302}S(O)_2$- wherein R_{302} is a heterocyclic group.

The term "arylsulfonylalkyl" as used herein refers to an arylsulfonyl group appended to a loweralkyl radical.

The term "aryl" as used herein refers to a monocylic or bicyclic carbocyclic ring system having one or more aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl and the like; or "aryl" refers to a heterocyclic aromatic ring as defined herein. Aryl groups can be unsubstituted or substituted with one, two or three substituents independently selcted from loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide.

The term "substituted phenyl" as used herein refers to a phenyl ring substituted with one, two or three substituents chosen from the group loweralkoxy, loweralkyl, amino, loweralkylamino, hydroxy, halo, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxy, carboalkoxy and carboxamide, including, but not limited to halophenyl, loweralkylphenyl, alkoxyphenyl and the like.

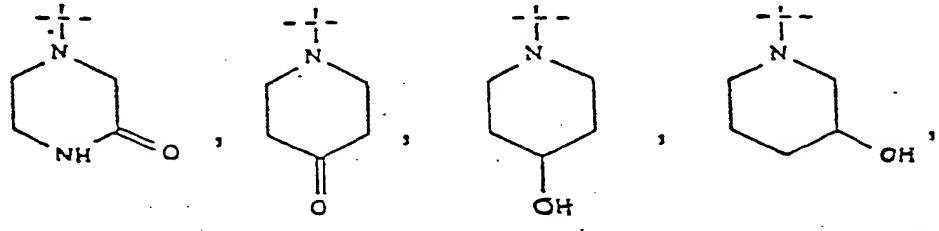
The term "substituted naphthyl" as used herein refers to a naphthyl ring substituted with one, two or three substituents chosen from the group loweralkoxy, loweralkyl, amino, loweralkylamino, hydroxy, halo, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxy, carboalkoxy and carboxamide, including, but not limited to halonaphthyl, alkoxynaphthyl and the like.

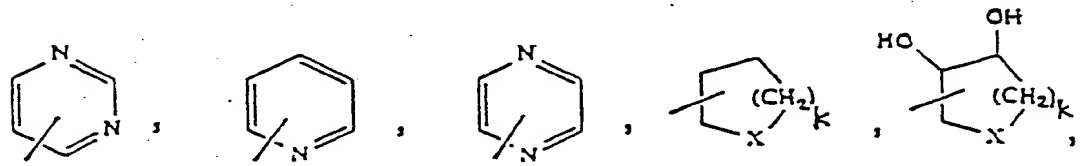
The term "alkylaryl" as used herein refers to a loweralkyl group appended to an aryl radical.

The term "heterocylcic group" or "heterocyclic" as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from oxygen, sulfur and nitrogen, or a 5- or 6-membered ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; wherein the 5-membered ring has 0 to 2 double bonds and the 6-membered ring has 0 to 3 double bonds; wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, wherein the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring. Heterocyclics in which nitrogen is the heteroatom are preferred. Fully saturated heterocyclics are also preferred. Preferred heterocyclics are: pyrryl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, N-methylpiperazinyl, azetidinyl, N-methylazetidinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, triazolyl and benzothienyl.

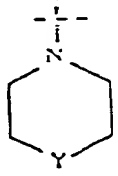
Heterocyclics can be unsubstituted or monosubstituted or disubstituted with substituents independently selected from hydroxy, halo, oxo (=O), alkylimino (R*N= wherein R* is a loweralkyl group), amino, alkylamino, dialkylamino, alkoxy, thioalkoxy, polyalkoxy, loweralkyl, haloalkyl or cycloalkyl.

The most preferred heterocyclics include imidazolyl, pyridyl, piperazinyl, N-methylpiperazinyl, azetidinyl, N-methylazetidinyl, thiazolyl, thienyl, triazolyl and the following:





wherein k is 1 or 2 and X is N, NH, O, or S, provided that X is the point of connection only when X is N,



wherein Y is NH, N-loweralkyl, O, S, or SO_2, or

wherein the symbols (i), (ii) and (iii) represent 5-membered heterocycles containing one or more heteroatoms and containing 2 double bonds; wherein Z_1 is N, O, or S and not the point of connection and Z_2

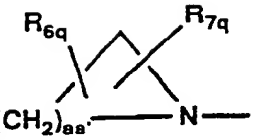
is N when it is the point of connection and NH, O or S when it is not the point of connection; with the proviso that when Z_2 is the point of connection, then Z_1 is N.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures or to prevent the attack of exopeptidases on the compounds or to increase the solubility of the compounds and includes but is not limited to sulfonyl, acyl, acetyl, pivaloyl, t-butyloxycarbonyl (Boc), carbonylbenzyloxy (Cbz), benzoyl or an L- or D- aminoacyl residue, which may itself be N-protected similarly.

The term "O-protecting group" as used herein refers to a substituent which protects hydroxyl groups against undesirable reactions during synthetic procedures and includes but is not limited to substituted methyl ethers, for example methoxymethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, benzyl and triphenylmethyl; tetrahydropyranyl ethers; substituted ethyl ethers, for example, 2,2,2-trichloroethyl and t-butyl; silyl ethers, for example, trimethylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl; cyclic acetals and ketals, for example, methylene acetal, acetonide and benzylidene acetal; cyclic ortho esters, for example, methoxymethylene; cyclic carbonates; and cyclic boronates.

The term "substituted amino" as used herein refers to:
I) alkylamino,
II) dialkylamino,
III) (hydroxyalkyl)(alkyl)amino,
IV) (dihydroxyalkyl)(alkyl)amino,
V) alkoxycarbonylalkylamino,
VI) carboxyalkylamino,
VII) (amino)carboxyalkylamino,
VIII) ((N-protected)amino)carboxyalkylamino,
IX) (alkylamino)carboxyalkylamino,
X) ((N-protected)alkylamino)carboxyalkylamino,
XI) (dialkylamino)caboxyalkylamino,
XII) (amino)alkoxycarbonylalkylamino,
XIII) ((N-protected)amino)alkoxycarbonylalkyl-amino,
XIV) (alkylamino)alkoxycarbonylalkylamino,
XV) ((N-protected)alkylamino)alkoxycarbonyl-alkylamino,
XVI) (dialkylamino)alkoxycarbonylalkylamino,
XVII) (alkoxyalkyl)(alkyl)amino,
XVIII) (alkoxyalkoxyalkyl)(alkyl)amino,
XIX) di-(alkoxyalkyl)amino,
XX) di-(alkoxyalkoxyalkyl)amino,
XXI) di-(hydroxyalkyl)amino,
XXII) ((unsubstituted heterocyclic)alkyl)(alkyl)-amino,
XXIII) ((substituted heterocyclic)alkyl)(alkyl)-amino,

XXIV)



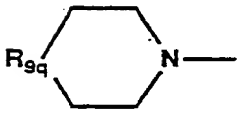
wherein aa' is 1 to 5 and R_{6q} and R_{7q} are independently selected from

1) hydrogen,
2) hydroxy,
3) alkoxy,
4) thioalkoxy,
5) alkoxyalkoxy,
6) carboxy,
7) alkoxycarbonyl,
8) halogen,
9) amino,
10) alkylamino,
11) dialkylamino,
12) alkylsulfonylamino,
13) arylsulfonylamino,
14) alkylaminocarbonylamino,
15) alkylaminocarbonyloxy,
16) alkoxycarbonyloxy,
17)

wherein dd' is 1 to 5,
and
18) R_{8q}-Z_q- wherein
Z_q is O, S or NH and R_{8q} is a C_1 to C_6

straight or branched carbon chain substituted by a substituent selected from hydroxy, alkoxy, thioalkoxy, alkoxyalkoxy, amino, alkylamino, dialkylamino, carboxy, alkoxycarbonyl, aryl and heterocyclic;

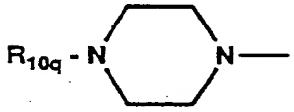
XXV)



wherein R_{9q} is

1) O,
2) S,
3) SO_2 or
4) C=O; or

XXVI)



wherein R_{10q} is

1) hydrogen,
2) loweralkyl,
3) an N-protecting group or
4) R_{11q}-C(O)- wherein R_{11q} is aminoalkyl, (N-protected)aminoalkyl, 1-amino-2-phenylethyl or 1-(N-protected)amino-2-phenylethyl.

The term "substituted methylene group" as used herein refers to:

(I) $-CHR_{13q}R_{14q}$ wherein

1) R_{13q} is

i) hydrogen or
ii) hydroxy

and

2) R_{14q} is
i) hydrogen,
ii) loweralkyl,
iii) hydroxy,
iv) hydroxyalkyl,
v) alkoxy,
vi) alkoxyalkyl,
vii) azido,
viii) azidoalkyl,
ix) amino,
x) (N-protected)amino,
xi) aminoalkyl,
xii) (N-protected)aminoalkyl,
xiii) alkylamino,
xiv) (N-protected)(alkyl)amino,
xv) alkylaminoalkyl,
xvi) (N-protected)(alkyl)-
aminoalkyl,
xvii) dialkylamino,
xviii) dialkylaminoalkyl,
xix) carboxyalkyl,
xx) thioalkoxy,
xxi) thioalkoxyalkyl,
xxii) alkylsulfonyl,
xxiii) alkylsulfonylalkyl,
xxiv) thioaryloxy,
xxv) thioaryloxyalkyl,
xxvi) arylsulfonyl,

xxvii) arylsulfonylalkyl,
xxviii) (unsubstituted heterocyclic)alkyl or
xxvix) (substituted heterocyclic)alkyl

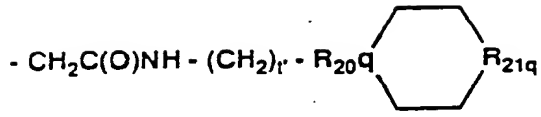
such that when R_{13q} is hydroxy then R_{14q} is not hydroxy, alkoxy, azido, amino, alkylamino, dialkylamino, (N-protected)amino, (N-protected)(alkyl)amino, thioalkoxy, alkylsulfonyl or arylsulfonyl, and such that when R_{13q} is hydrogen then R_{14q} is not hydrogen or loweralkyl;

(II) $-C(=CH_2)C(O)NHR_{15q}$;
(III) $-C(OH)(R_{16q})C(O)NHR_{15q}$ or
(IV) $-CH(R_{16q})C(O)NHR_{15q}$ wherein

1) R_{15q} is
i) loweralkyl,
ii) hydroxyalkyl,
iii) alkoxyalkyl,
iv) aminoalkyl,
v) alkylaminoalkyl,
vi) dialkylaminoalkyl,
vii) aryl,
viii) heterocyclic or
ix) (heterocyclic)alkyl and

2) R_{16q} is
i) hydrogen,
ii) loweralkyl,
iii) hydroxyalkyl,
iv) haloalkyl or
v) azidoalkyl;

(V)



wherein

1) t' is 0 to 3,

2) R_{20q} is

i) CH_2 or

ii) N and

3) R_{21q} is

i) NH,

ii) O,

iii) S or

iv) SO_2,

such that when t' is 0 then R_{20q} is CH_2 and when t' is 1 to 3 then R_{20q} is N,

(VI) $-CH_2CH(R_{22q})C(O)NHR_{23q}$ wherein

1) R_{22q} is

i) loweralkyl or

ii) cycloalkylalkyl

and

2) R_{23q} is

i) loweralkyl,

ii) hydroxyalkyl,

iii) alkoxyalkyl,

iv) aminoalkyl,

v) alkylaminoalkyl,

vi) dialkylaminoalkyl,

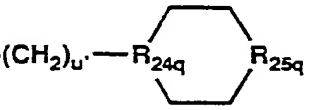
vii) aryl,

viii) arylalkyl

ix) heterocyclic,

x) (heterocyclic)alkyl or

xi)



wherein

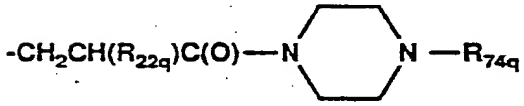
a) u' is 0 to 3,

b) R_{24q} is CH_2 or N and

c) R_{25q} is NH, O, S or SO_2,

such that when u' is 0 then R_{24q} is CH_2 and when u' is 1 to 3 then R_{24q} is N;

(VII)



wherein

1) R_{22q} is as defined above and

2) R_{74q} is

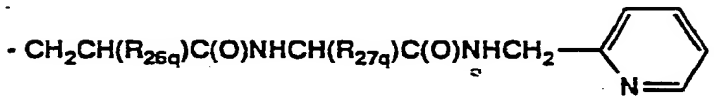
i) hydrogen,

ii) loweralkyl,

iii) an N-protecting group or

iv) R_{75q}-C(O)- wherein R_{75q} is aminoalkyl or (N-protected)-aminoalkyl;

(VIII)



wherein

1) R_{26q} is

i) loweralkyl or

ii) cycloalkylalkyl and

2) R_{27q} is

i) loweralkyl or

ii) cycloalkylalkyl;

(IX) $-CH_2CH(R_{81q})NHC(O)R_{82q}$ or $-CH_2CH(R_{81q})NHS(O)_2R_{82q}$ wherein

1) R_{81q} is

i) loweralkyl or

ii) cycloalkylalkyl and

2) R_{82q} is

i) loweralkyl,

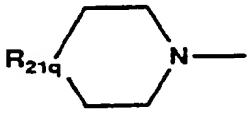
ii) alkoxy,

iii) alkylamino,

iv) dialkylamino,

v) -OR* wherein R* is aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl or (heterocyclic)alkyl or

vi)



wherein R_{21q} is as defined above;

(X) $-CH_2NHC(O)R_{82q}$ or $-CH_2NHS(O)_2R_{82q}$ wherein R_{82q} is as defined above; or

(XI) $-CF_2CH(OH)R_{83q}$ wherein R_{83q} is loweralkyl, loweralkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl,

cycloalkyenylalkyl, aryl, aryalkyl, heterocyclic or (heterocyclic)alkyl.

The terms "lipophilic or aromatic amino acid side chains" as used herein refer to amino acid side chains selected from the group isobutyl, isopropyl, sec-butyl, benzyl, p-methoxybenzyl, imidazole-4-yl-methyl, p-hydroxybenzyl, 1- and 2-naphthylmethyl, (pyrazolyl)methyl, (thiazolyl)methyl, cyclohexylmethyl, (3-indolyl)methyl, CH_3SCH_2- and the like. General references to amino acid side chains in both the description and claims herein is to be taken as reference to such, whether naturally occurring in proteins or not, and to both D- and L- forms.

The terms "Ala", "His", "Leu", "Phe", "Tyr", "Cys", "Gly", "Lys", "Sar", "Pro", "HomoPhe" and "norLeu" as used herein refer to alanine, histidine, leucine, phenylalanine, tyrosine, cysteine, glycine, lysine, sarcosine, proline, homophenylalanine and norleucine, respectively. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature for amino acids and peptides (Eur. J. Biochem. 1984, 158, 9-31).

The chiral centers of the novel renin inhibiting compounds of the invention may have either the "R", "S" or "R,S" configuration. The terms "S" and "R" configuration are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-30.

Renin inhibitors having the general structure shown in group (9) can be prepared as shown in Schemes IA-XXIIIA. The syntheses of segments containing substituents D are described in the Examples or have previously been described (Kempf, et al., J. Med. Chem. 1987, 30, 1978; Luly, et al., J. Med. Chem. 1987, 30, 1609; Buhlmayer, et al., U.S. Patent No. 4,727,060; Morisawa, et al., European Patent Application No. 0228192; Ten Brink, PCT Patent Application No. WO87/02986).

In particular, the process shown in Scheme IA discloses the preparation of compounds of the invention having the general structure (1) wherein A is carboxy or alkoxycarbonyl and X is NH. As illustrated in Scheme IA, reductive amination of an amino acid ester (I) with an alpha-keto ester (II, R=loweralkyl) provides a diastereomeric mixture which is separated. Each of the diastereomers is hydrolyzed and coupled to the amine (VI) using standard peptide coupling reagents such as N-methylmorpholine (NMM), 1-hydroxybenzotriazole (HOBT) and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide (EDAC) to give the desired compound (VII).

Compound (VII) can also be prepared using the following method. After reductive amination of (II) with (I), the diastereomeric mixture is hydrolyzed to give (III) and then coupled to amine (VI) as described above. The mixture of diastereomers is then separated, providing two separate isomers. Compound (VII) may be further hydrolyzed to the acid (VIII). The assignment of R or S configuration to the carbon bearing the R_3 substituent in compound (VIII) is based on the fact that the compound derived from the L-

the L-isomer is generally a more potent renin inhibitor than the compound derived from the corresponding D-isomer.

The stereochemistry at the chiral carbons of (VIII) can also be established by using chiral starting materials. As illustrated in Scheme IIA, chiral amino acid ester (XV, R=loweralkyl) is reacted with chiral D-trifluorosulfonyloxy ester (XVI) to give the single isomer (XVII) which is then hydrolyzed and coupled to (VI) to obtain the desired compound (XVIII).

Alternatively, Scheme IIIA illustrates the preparation of compounds (XI). Reductive amination of (IX, R_2=loweralkyl) by (X) provides a mixture of diastereomers which can be separated.

A further alternative illustrated by Scheme IIIA involves reductive amination of (IX, R_2=loweralkyl) by (XII) followed by separation of the diastereomers (XIII). Each of the diastereomers is then debenzylated and coupled to (VI) as previously described. The methods of Scheme III provide compound (XI) having unknown stereochemistry at the carbon bearing the R_1 substituent.

The process of Scheme IVA discloses the preparation of compounds of the general structure (1) wherein A is a carboxy derivative R_5CO- wherein R_5 is an amine and X is NH. Selective hydroysis of one of the diastereomers (IV) gives the acid derivative (XIX). The acid (XIX) is coupled to the amine R_5-H and the resulting amide-ester is hydrolyzed to give (XXI). The acid (XXI) is coupled to amine (VI) to give (XXII).
Alternatively, compound (VIII) can be coupled to amine (VI) to provide (XXII).

The process in Scheme VA discloses the preparation of compounds of the general structure (XXV) wherein R_{28} is a C_1 to C_4 straight or branched carbon chain substituted by a substituent selected from carboxy, alkoxycarbonyl, alkylsulfonyl or a substituted or unsubstituted heterocylic. A reaction sequence similar to that used in Scheme I is followed except that compound (XXIII) is employed instead of the amino acid ester (I).

The process in Scheme VIA discloses the preparation of compounds of general structure (XXIX) wherein A is alkoxycarbonyl or R_5CO- wherein R_5 is a substituted amine and X is O or S. The reaction of an alcohol or thiol (XXVI) with the bromo-acid (XXVII) provides a single diastereomer (XXVIII) which is then coupled to the amine (VI) using standard peptide coupling conditions to give the desired product (XXIX). If the racemic form of the bromo-acid (XXVII) is used, diastereomer separation can take place with compound (XXVIII) or (XXIX).

Scheme VIIA discloses the preparation of compounds of general structure (1) wherein X is CH_2 and A is R_5CO- wherein R_5 is hydroxy, alkoxy, thioalkoxy or an amine. Compound (XXX) (J. Med. Chem. 26 1277 (1983)) is coupled to amine (VI) to provide the amide ester (XXXI) which is hydrolyzed to give the carboxylic acid (XXXII). Coupling to the appropriate amine provides (XXXIII) wherein R_5 is a substituted amine.

The process in Scheme VIIIA discloses the preparation of compounds of the general structure (1) wherein X is CHOH. Aldol condensation of an aldehyde (XXXIV) (J. Am. Chem. Soc. 103 2876 (1981)) with the chiral oxazolidinone imide (XXXV) (J. Am. Chem. Soc. 103 2127 (1981)) provides

(XXXVI). After protection of the secondary alcohol, the benzyl group is removed and the primary alcohol oxidized to the carboxylic acid (XXXVII). The acid is coupled to the appropriate amine R_5-H, the imide is hydrolyzed, the resulting acid is coupled to the amine (VI) and the alcohol is deprotected providing the desired compound (XXXVIII).

Schemes IXA-XIIIA disclose the preparation of intermediates used in Schemes IA, VA and VIA, respectively. In Scheme XA, R is loweralkyl. In Scheme XIA, R is loweralkyl, Ts is p-toluenesulfonyl and P is an N-protecting group. In Scheme XIIA, R is loweralkyl, R_5-H is an amine and X is O or S. In Scheme XIIIA, R_5-H is an amine.

The process in scheme XIVA describes the preparation of compounds of the general structure XLII wherein R_3 is a C_1 to C_6 straight or branched alkyl/alkenyl carbon chain or heteroatom substituted carbon chain substituted by O, S, N or substituted by a substitutent selected from a heterocycle or substituted heterocycle. R_1 is selected from aryl, substituted aryl, heterocycle, substituted heterocycle, cycloalkyl, unsaturated cycloalkyl, alkylaryl, alkylheterocycle, alkyl cycloalkyl, alkyl unsaturated cycloalkyl. R_5 is a cyclic amine, substituted amine, substituted cyclic amine, aryl, substituted aryl, heterocycle, substituted heterocycle. The synthesis of intermediate XL begins by the metalation of the sulfonyl derivative XXXIX with alkyl lithium reagents in THF or THF/HMPA at low temperature according to the procedure sited in European Patent Application No. EP0309841, published April 5, 1989. The subsequent anion is trapped with the appropriate 2-substituted-3-benzyloxypropyl

iodide (prepared from the alcohlol by the procedure of M. Holladay; J. Med. Chem. 1983, 26, 1277), p-toluenesulfonyl chloride and sodium iodide. The resulting diastereomeric sulfonyl ethers XL are deprotected (H_2 Pd/C or PdOH) and oxidized to the corresponding carboxylic acids XLI using a variety of oxidants ($KMnO_4$, Jones, PDC, RuO_4, Pt/O_2). Coupling of the acids with mimics of the Leu-Val cleavage site of angiotensinogen (T-H) using standard coupling procedures gives the diastereomeric amides XLII and XLIII which are separated to give optically active inhibitors.

Scheme XVA outlines the synthesis of carboxylic acids of the general formula XLIX wherein R_1 is a C_1 to C_6 straight or branched alkyl/alkenyl carbon chain or heteroatom substituted carbon chain substituted by O, S, N. or substituted by a substitutent selected from a heterocycle or substituted heterocycle. R is selected from aryl, substituted aryl, heterocycle, substituted heterocycle, cycloalkyl, unsaturated cycloalkyl, alkylaryl, alkylheterocycle, alkyl cycloalkyl, alkyl unsaturated cycloalkyl. The cyclic amine (n" = 1 to 7) is substituted with groups V selected from a C_1 to C_6 straight or branched alkyl/alkenyl carbon chain or heteroatom substituted carbon chain substituted by O, S, N. The synthesis begins by esterificaton followed by allylation of the 2S-hydroxyacid XLIV. Ester XLV is reduced with lithium aluminum hydride and the resulting alcohol is reacted with ozone. Reductive workup of the ozonide and Collins oxidation ($CrO_3 \cdot 2Pyr$) gives the optically pure lactone XLVI. Reaction of the lactone with LiHMDS in THF or THF/HMPA followed by the addition of

R_1-I or R_1-Br (i.e., an alkyl iodide or arylalkyl iodide or bromide) gives the disubstituted lactone XLVII. The lactone XLVII is reacted with the amino aluminum reagent which is prepared from the secondary amine and trimethylaluminum according to the procedure of Weinreb et. al. Org. Syn. 1980, 59, 49, to give the alcohol XLVIII. Oxidation of the alcohol using a variety of oxidants ($KMnO_4$, Jones, PDC, RuO_4, Pt/O_2) gives the acid XLIX which is ready for coupling to T-H using known methods.

An alternative synthesis of the disubstituted lactone LIII and related lactone LVII is shown in scheme XVIA. The 2(S)-hydroxyacid L is first converted to the ethyl ester by Fisher esterification. Trans esterification with the Z-allylic alcohol and titanium isopropoxide (using the procedure of Seebach et. al. Org. Syn. 1986, 65, 230) gives the hydroxy ester LI. Halo (I_2 or NBS) or mercuric trifluoroacetate cyclization of the hydroxy olefin gives the disubstituted lactone LII. Reduction of LII with tributyltinhydride or sodium borohydride affords the reduced lactone intermediate LIII.

Scheme XVIIA discloses an alternative synthesis of carboxylic acids LVIII and LIX wherin R_1 is a C_1 to C_6 straight or branched alkyl/alkenyl carbon chain or heteroatom substituted carbon chain substituted by O, S, N or substituted by a substitutent selected from a heterocycle or substituted heterocycle. R is selected from aryl, substituted aryl, heterocycle, substituted heterocycle, cycloalkyl, unsaturated cycloalkyl, alkylaryl, alkylheterocycle, alkyl cycloalkyl, alkyl unsaturated cycloalkyl. The cyclic amine (n" = 1 to 7) is

substituted with groups V selected from a C_1 to C_6 straight or branched alkyl/alkenyl carbon chain or heteroatom substituted carbon chain substituted by O, S, N. The synthetic strategy is similar to that outlined in scheme XVA. The lactone LV is prepared from the corresponding amino alcohol LIV. Alkylation of LV with NaHMDS and alkyl iodide or bromide gives the disubstituted lactone LVI. The lactone LVI is hydrolyzed and esterified to hydroxy ester LVII which is converted to the acid LIX as shown in the scheme. Alternatively, LVI is transformed to the acid LVIII. Carboxylic acids LVIII and LIX are converted to final inhibitor compounds LVIIIa and LIXa as previously described.

Scheme XVIIAa discloses a synthetic route to inhibitors containing esters of the general formula LVIb and LVIIb wherein R and R_1 are the same as previously described for scheme XVIIA and R_2 is selected from C_1 to C_6 straight or branched carbon chain. T is selected from a variety of mimics of the Leu-Val cleavage site of angiotensinogen. The five step sequence from LVI to LVIb prepares the key acid intermediate from permanganate oxidation which is coupled to give final products. The seven step sequence from LVI to LVIIb produces a similar final product with the R and R_1 substituents reversed.

The syntheses of hydroxyethylene dipeptide isosteres are depicted in Schemes XVIIIA and XIXA. The chirality of the valine-mimic isopropyl group is established via a highly diastereoselective aldol condensation. Scheme XVIIIA details the use of technology developed by D. A. Evans and coworkers (see D. A. Evans, J. Bartroli and T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127), in which the

aldehyde LX (synthesized in analogy to the isobutyl-substituted aldehyde described by S. Thaisrivongs, D. T. Pals, L. T. Kroll, S. R. Turner and F.-S. Han, *J. Med. Chem.* **1987**, *30*, 976) is condensed with the norephedrine-derived acyloxazolidinone to produce the aldol product LXI. Barton deoxygenation (D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574) provides the diprotected hydroxyethylene dipeptide isostere LXIII. Removal of the chiral auxiliary with basic peroxide (D. A. Evans, T. C. Britton and J. A. Ellman, *Tetrahedron Lett.* **1987**, *28*(49), 6141) affords the intermediate carboxylic acid LXIV, which is then coupled to the desired amines (RNH_2) to yield amides LXV.

An alternative strategy is outlined in Scheme XIXA. Employment of the cysteine-derived thiazolidinethione (C. N. Hsiao, L. Liu and M. J. Miller, *J. Org. Chem.* **1987**, *52*, 2201) as chiral auxiliary allows the direct conversion of aldol adduct LXVII to the hydroxy amide LXVIII, thereby avoiding the hydrolysis step in Scheme XVIIIA. The secondary hydroxyl group is deoxygenated to produce the same protected amides LXV.

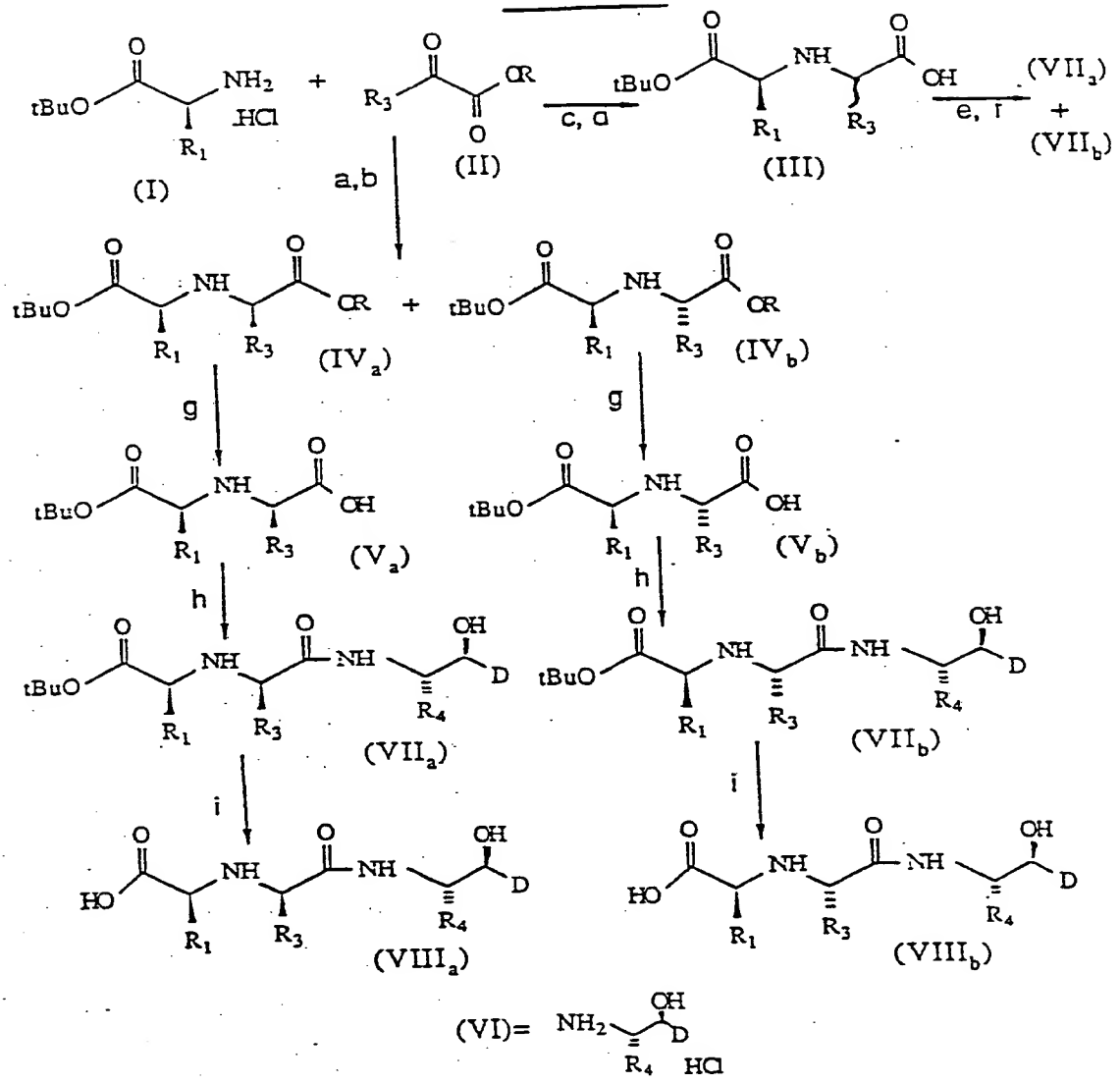
The synthesis of P_2' retro-inverted amine derivatives is described in Scheme XXA. The intermediate carboxylic acid LXIV is transformed into isocyanate LXX by the action of diphenylphosphorylazide, and the isocyanate is trapped with a range of nucleophiles, including, but not limited to primary and secondary amines, alcohols, thiols and organomagnesium halides. Scheme XXA illustrates the synthesis of retro-inverted amides LXXI, ureas LXXII and carbamates LXXIII.

These various hydroxyethylene dipeptide isosteres are then deprotected under the conditions listed in Scheme XXIA. The resulting free-base forms of the aminoalcohols LXXIV and LXXV are then available for standard peptide couplings.

Scheme XXIIA outlines a method for producing analogs of P2'-retro-inverted statine isosteres (an extension of the previous work of S. H. Rosenberg, J. J. Plattner, K. W. Woods, H. H. Stein, P. A. Marcotte, J. Cohen and T. J. Perun, *J. Med. Chem.* **1987**, *30*, 1224), in which the protected amino-epoxide LXXVI (J. R. Luly, J. F. Dellaria, J. J. Plattner, J. L. Soderquist and N. Yi, *J. Org. Chem.* **1987**, 52, 1487) is opened with a primary amine to provide aminoalcohols LXXVII. These compounds are then derivatized as sulfonamides, sulfamides, ureas, carbamates, amides or other amine derivatives. Scheme XXIIA details the example of a sulfonamide or sulfamide. The free aminoalcohol (LXXIX) is provided by simple deprotection of the Boc-group.

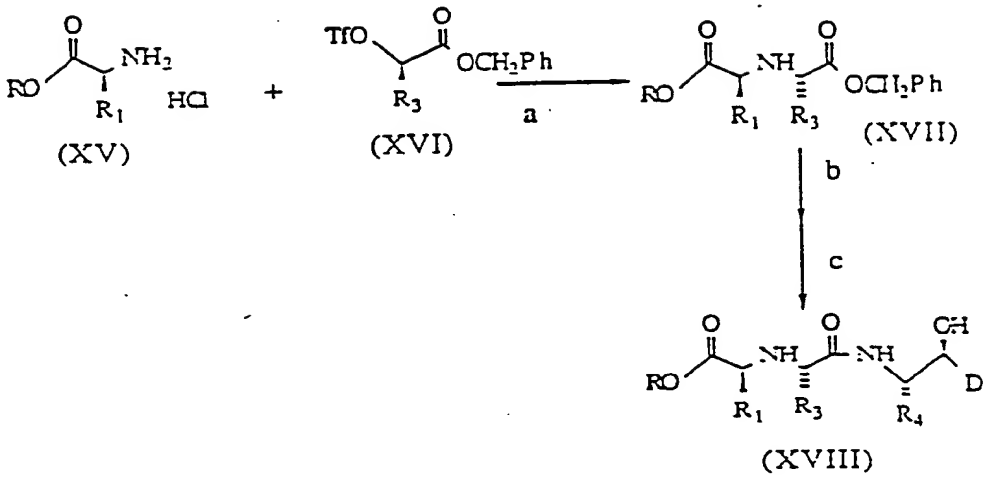
Scheme XXIIIA depicts an alternative strategy for the production of the P_2' retro-inverted amide derivatives. Intermediate aldehyde LX is condensed with a primary amine under standard reductive alkylation conditions, and the resulting amine LXXX is derivatized to the desired protected amine derivative LXXXII. This has been accomplished by the use of the appropriate sulfonyl or sulfamoyl chloride, to yield, respectively, the corresponding sulfonamide or sulfamide. In addition, the catechol sulfamate ester LXXXI can be employed to produce sulfamide derivatives. Deprotection produces aminoalcohols LXXXIII, available for coupling reactions.

SCHEME IA



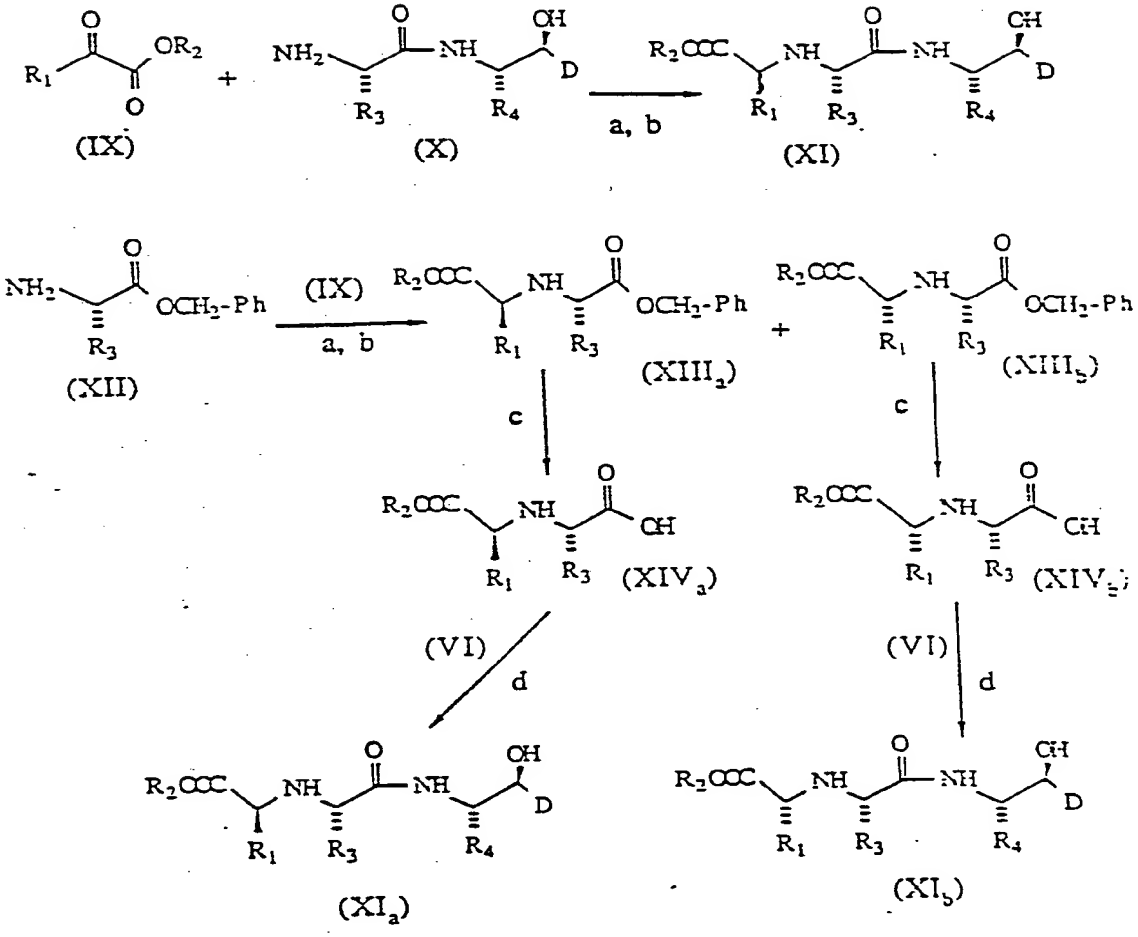
a: NaOAc, $NaCNBH_3$; b: separate diastereomers; c: as a; d: LiOH, H_2O, dioxane; e: (VI), NMM, HOBT, EDAC; f: as b; g: as d; h: as e; i: dioxane/HCl.

SCHEME II A



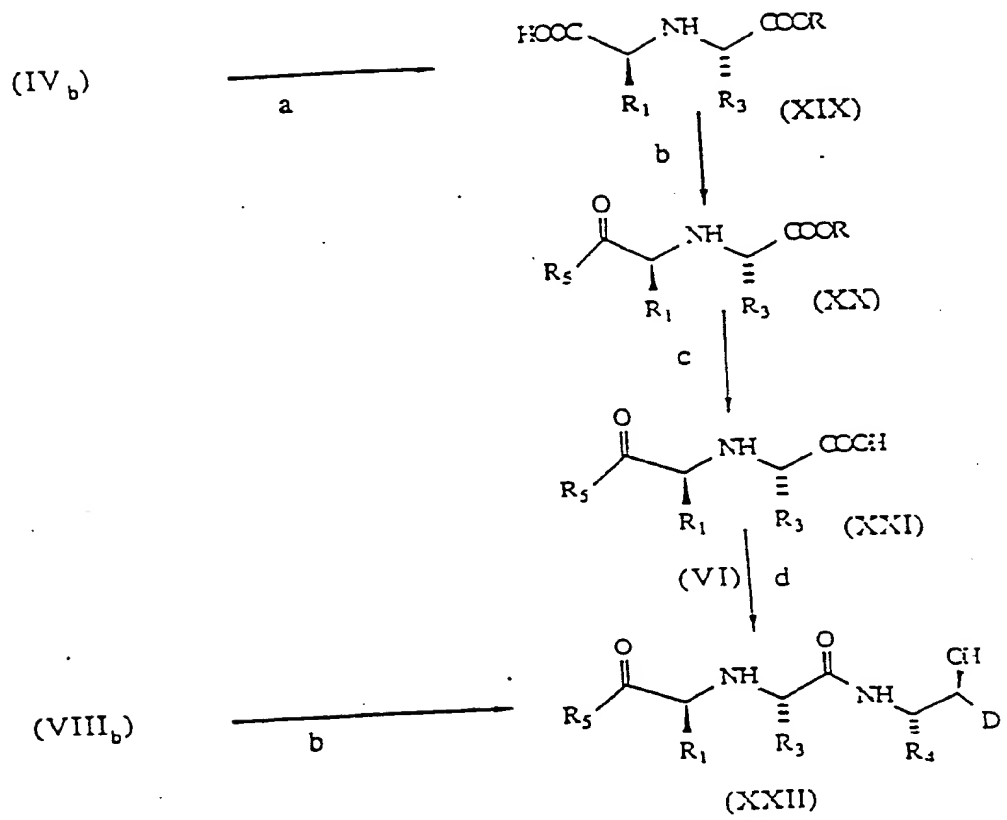
a: 2 eq TEA, CH_2Cl_2, 0-25°; b: selective hydrolysis;
c: coupled to (VI).

SCHEME III A



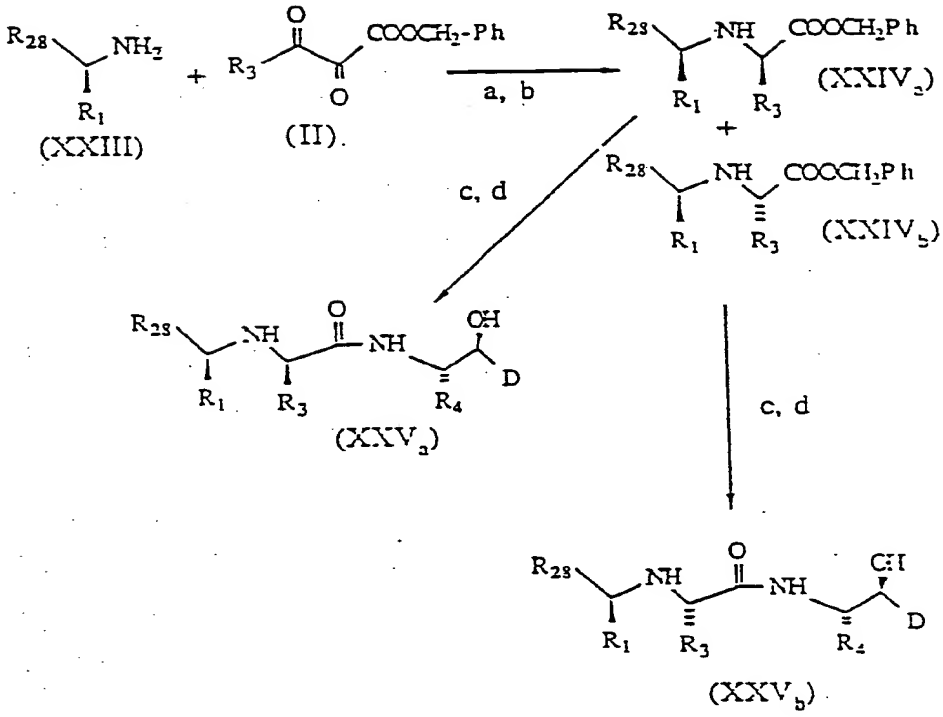
a: NaOAc, $NaCNBH_3$; b: separate diastereomers; c: H_2, Pd/C;
d: NMM, HOBT, EDAC

SCHEME IVA



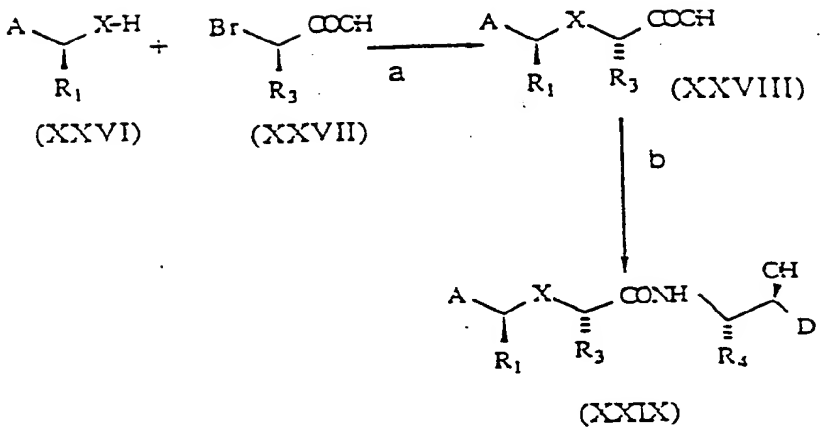
a: Dioxane/HCl; b: R_5-H, HOBT,EDAC; c: H_2,Pd/C or LiOH/H_2O;
d: NMM, HOBT,EDAC.

SCHEME VA



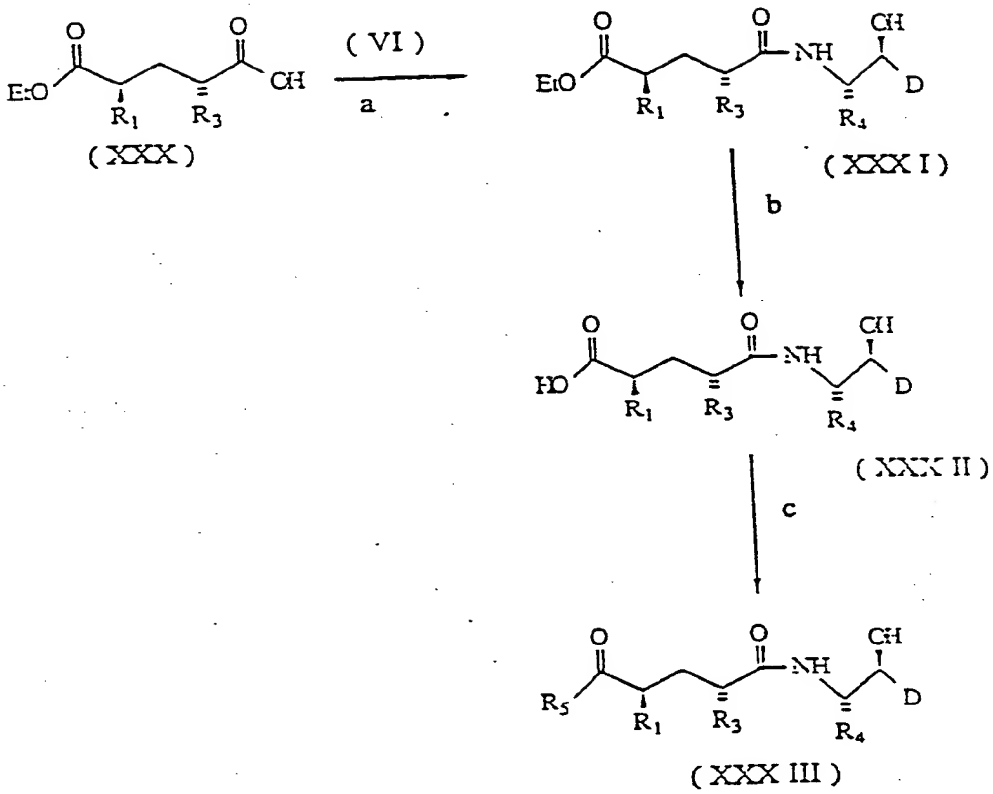
a: NaOAC, $NaCNBH_3$; b: separate diastereomers; c: H_2, Pd/C; d: (VI), NMM,HOBT, EDAC.

SCHEME VIA



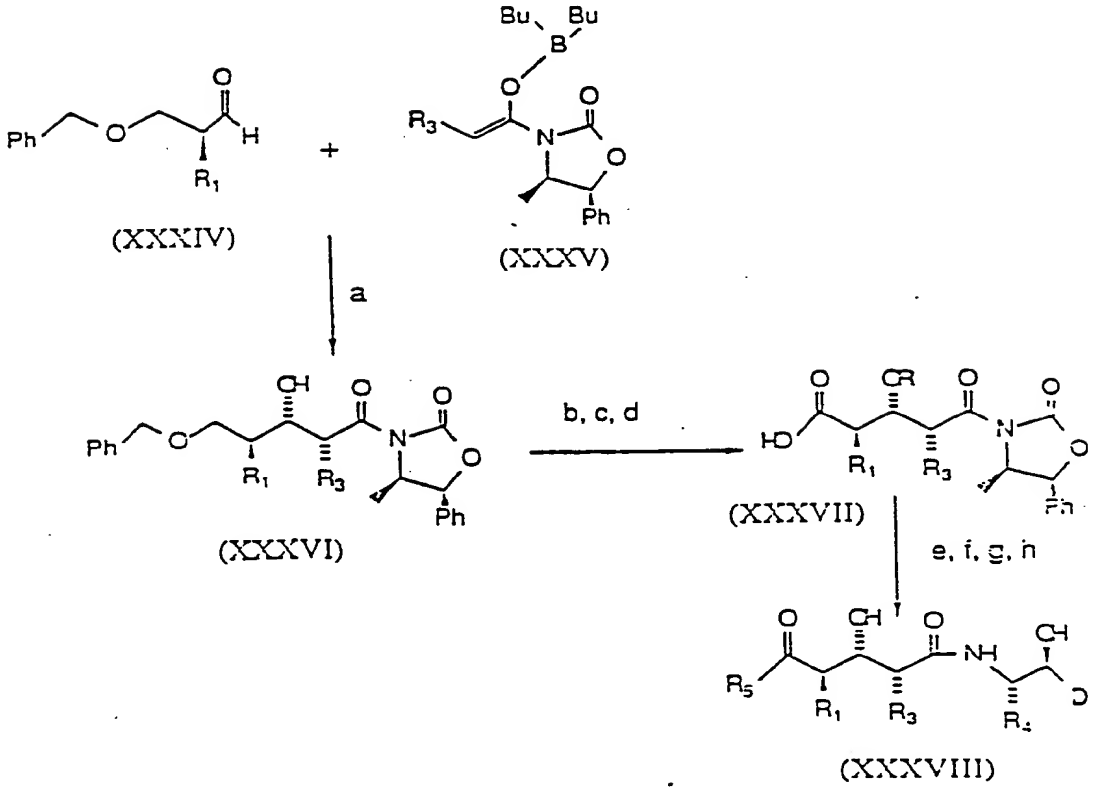
a: NaH, THF; b:(VI),NMM,HOBT,EDAC.

SCHEME VII A



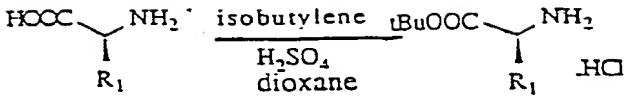
a: NMM, HOBT, EDAC; b: $LiOH/H_2O$/dioxane;
c: R_5-H, HOBT, EDAC.

SCHEME VIII A



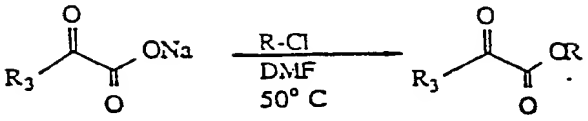
a: CH_2Cl_2, -72° C; b: protect; c: H_2, Pd/C;
d: Jones [O]; e: R_5-H, HOBT, EDAC; f: $LiOH/H_2O$;
g: (VI), HOBT, EDAC; h: deprotect.

SCHEME IX A



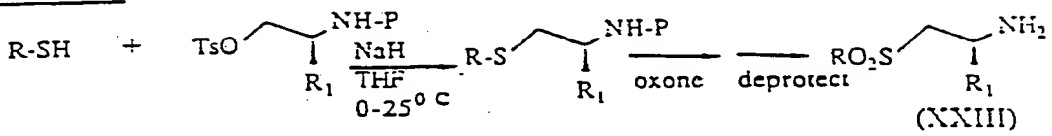
(I)

SCHEME X A

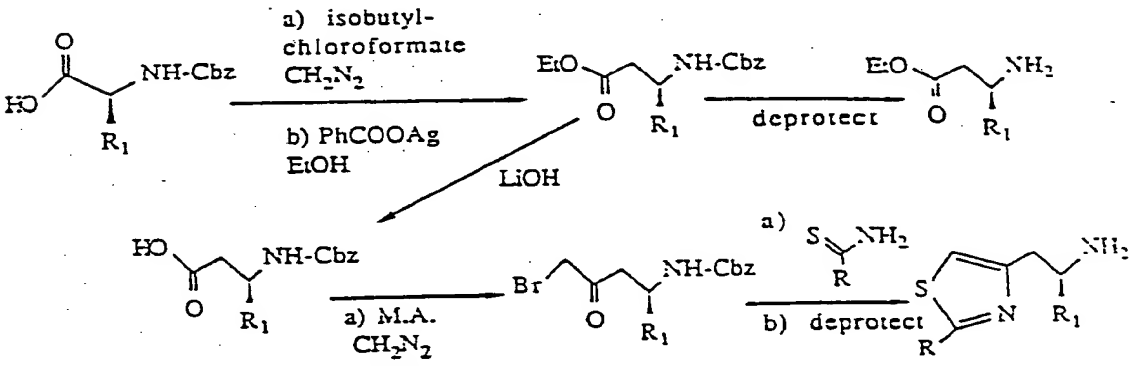


(II)

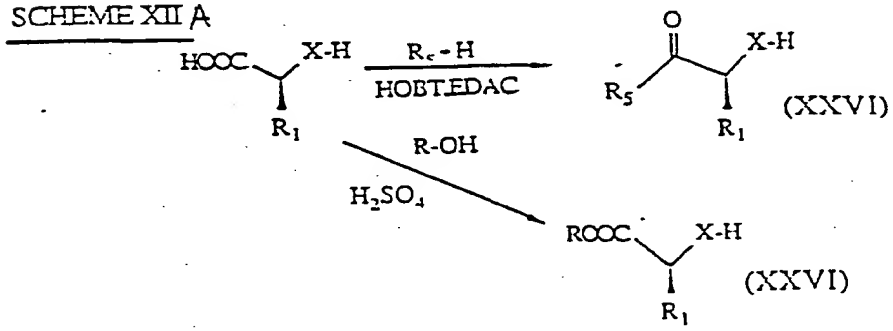
SCHEME XI A



(XXIII)



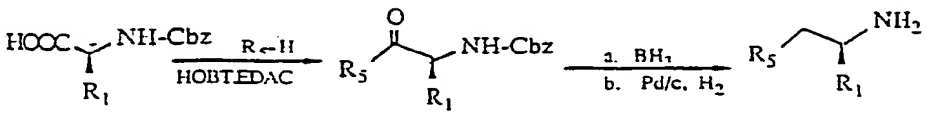
SCHEME XII A



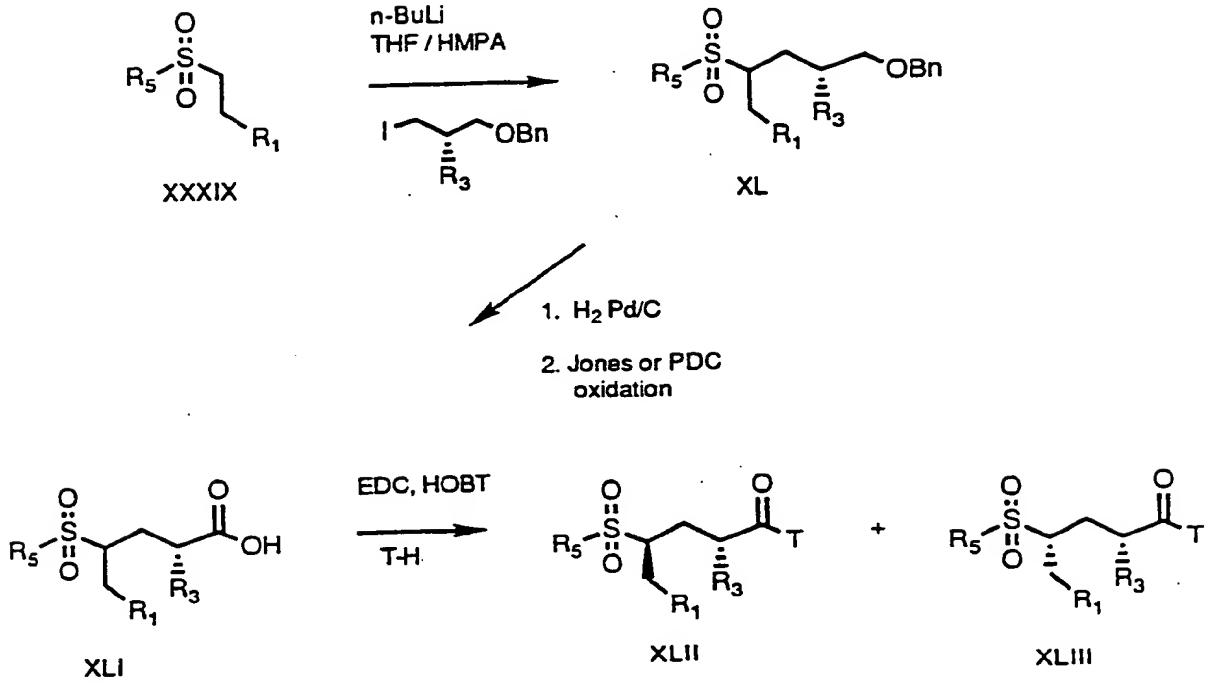
(XXVI)

(XXVI)

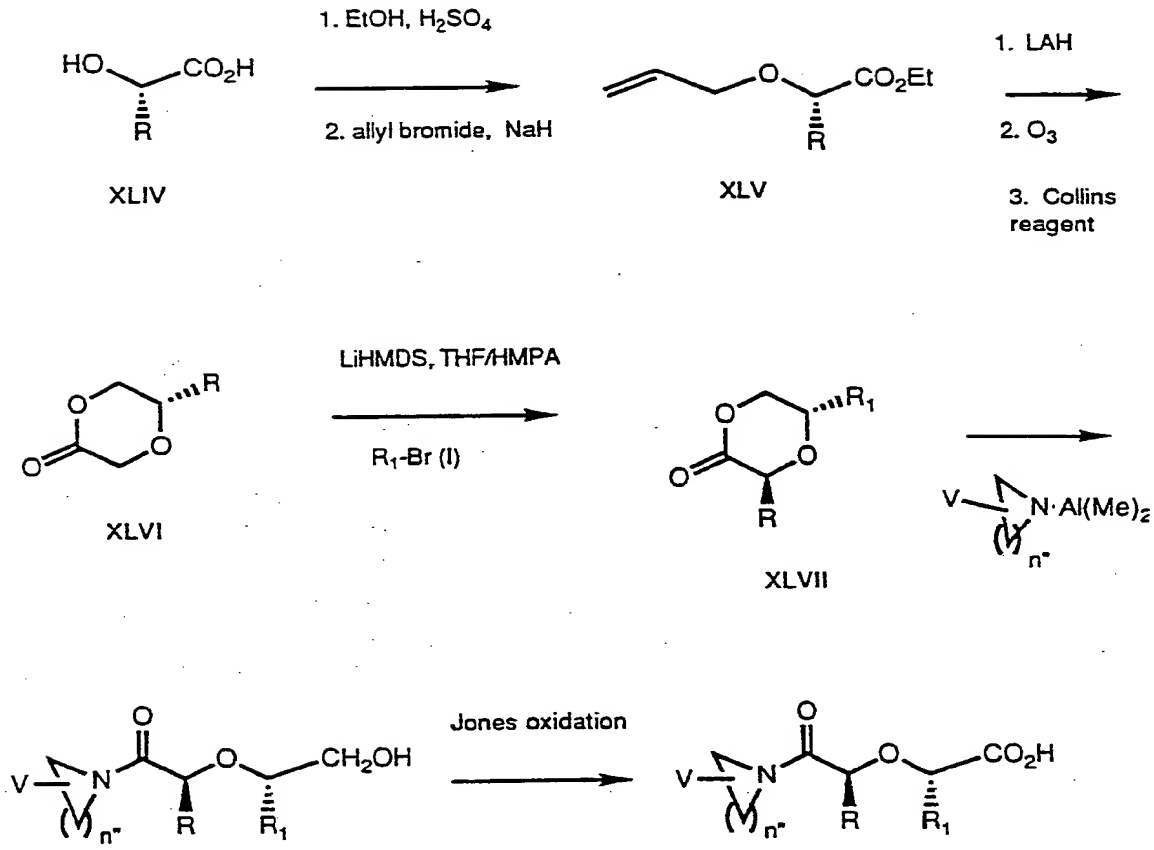
SCHEME XIII A



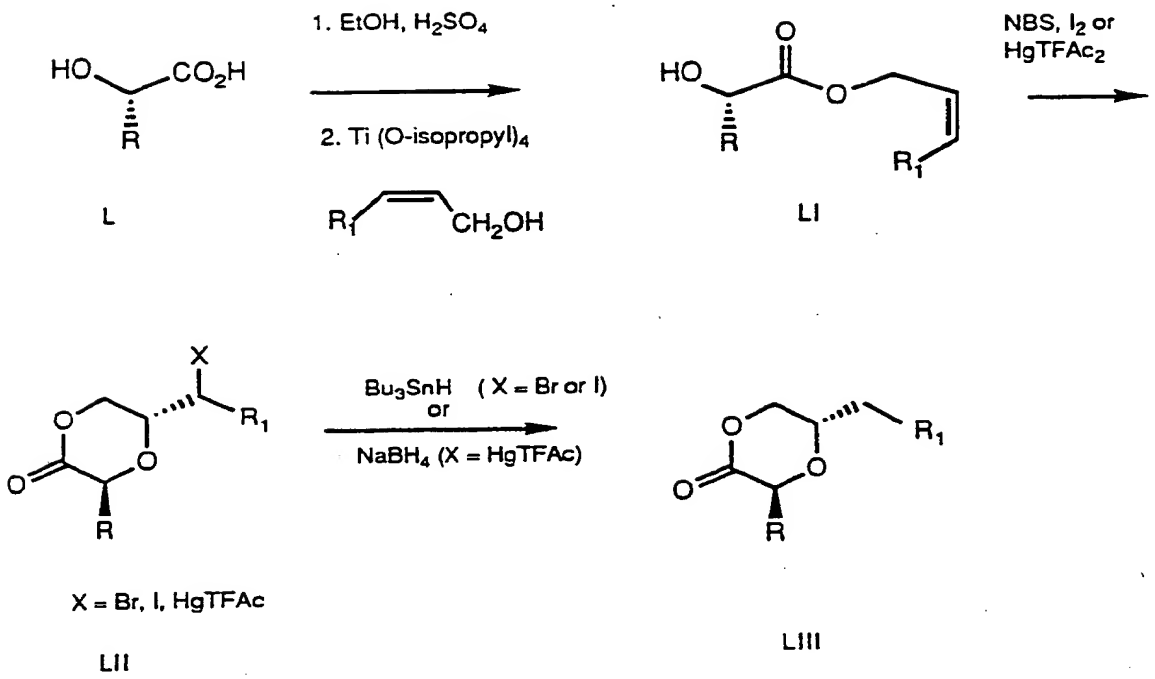
SCHEME XIVA


n-BuLi
THF / HMPA
OBn
XXXIX
XL
1. H_2 Pd/C
2. Jones or PDC oxidation
EDC, HOBT
T-H
OH
T
XLI
XLII
XLIII

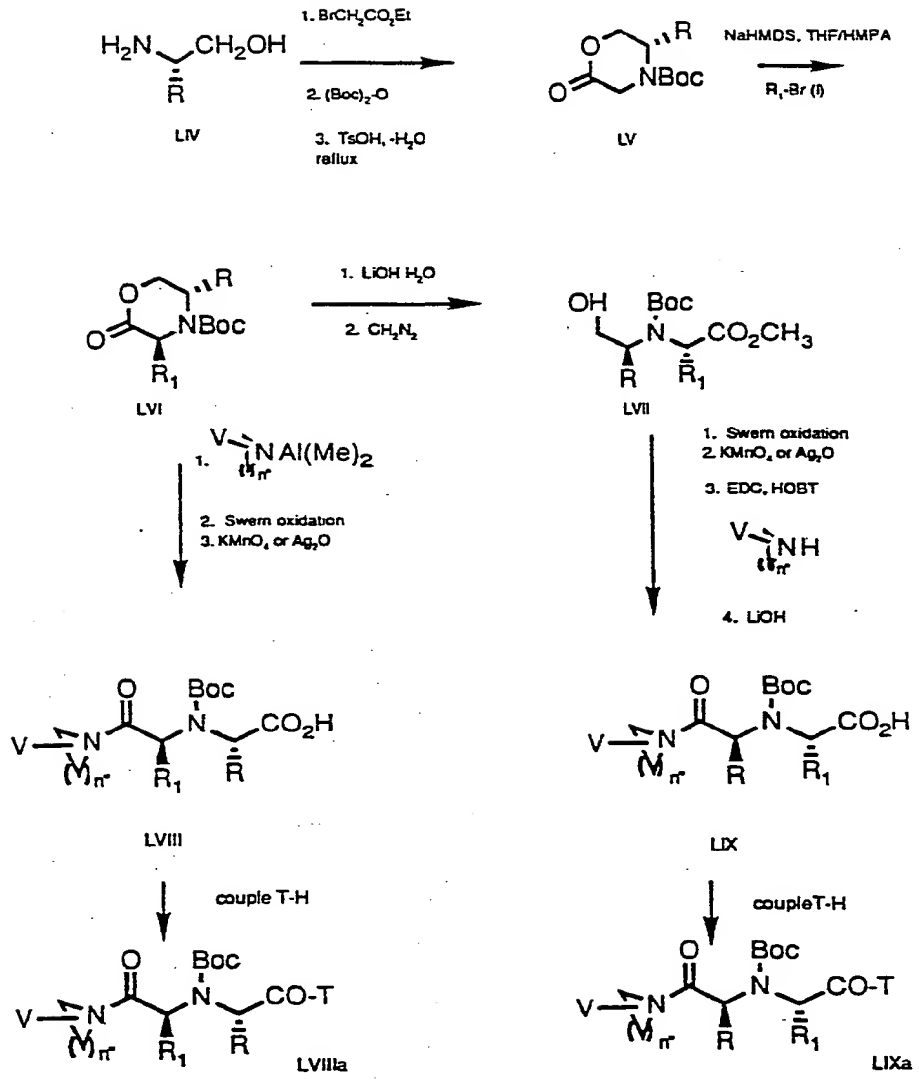
SCHEME XV A


1. EtOH, H_2SO_4
2. allyl bromide, NaH
1. LAH
2. O_3
3. Collins reagent
XLIV
XLV
LiHMDS, THF/HMPA
R_1-Br (I)
XLVI
XLVII
Jones oxidation

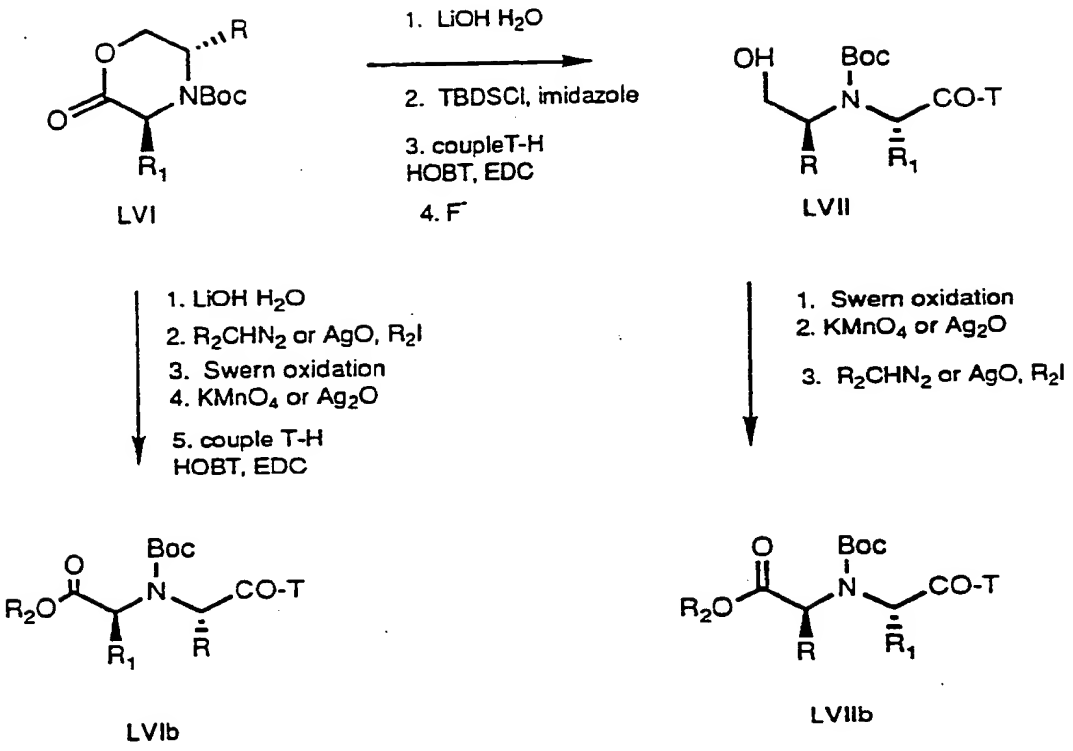
SCHEME XVI A


HO
CO2H
R
L
1. EtOH, H2SO4
2. Ti (O-isopropyl)4
R1
CH2OH
O
HO
O
R
R1
LI
NBS, I2 or
HgTFAc2
X
R1
O
O
O
R
X = Br, I, HgTFAc
LII
Bu3SnH (X = Br or I)
or
NaBH4 (X = HgTFAc)
R1
LIII

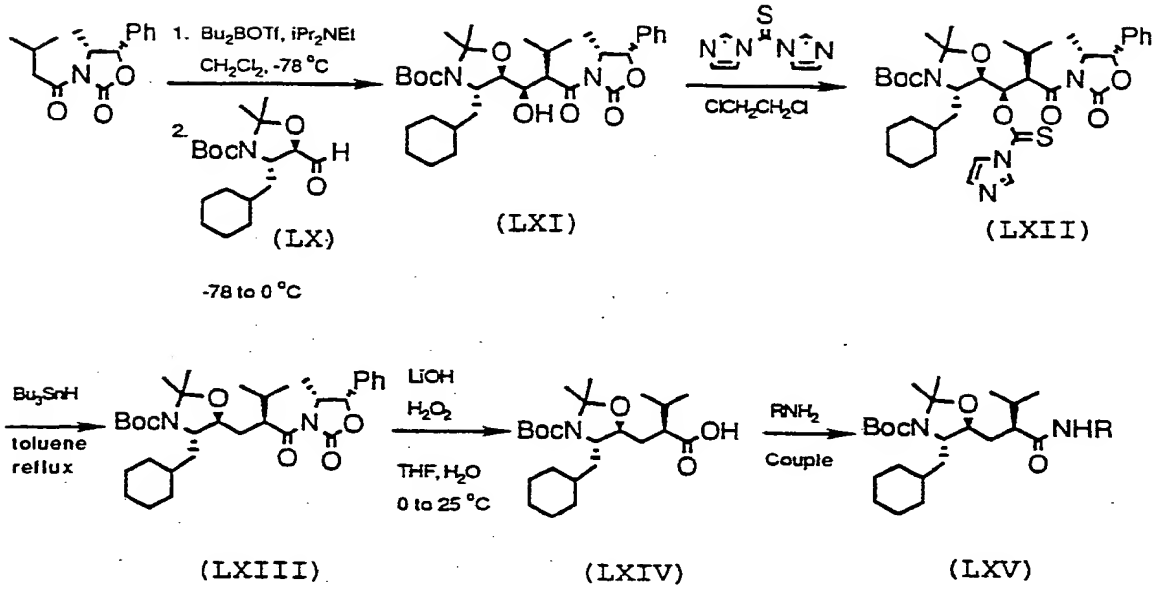
SCHEME XVII A



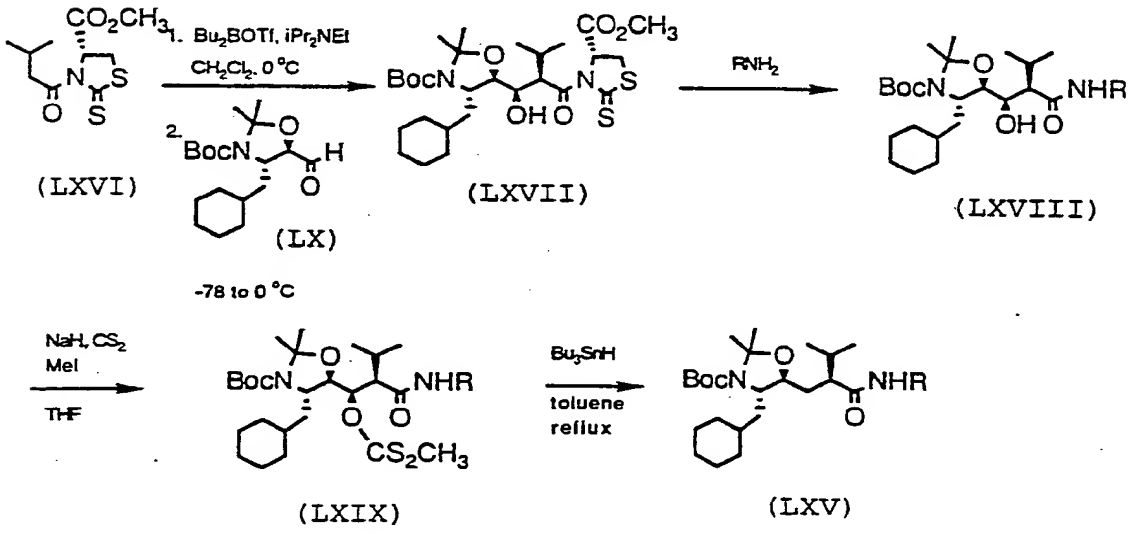
SCHEME XVII-Aa



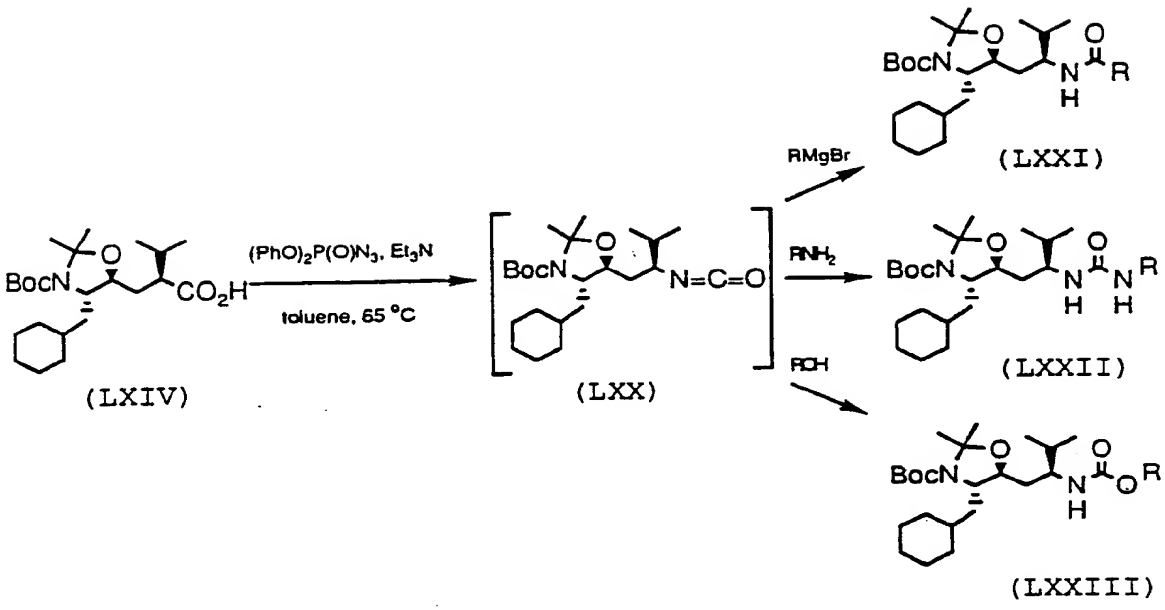
SCHEME XVIII A



SCHEME XIX A

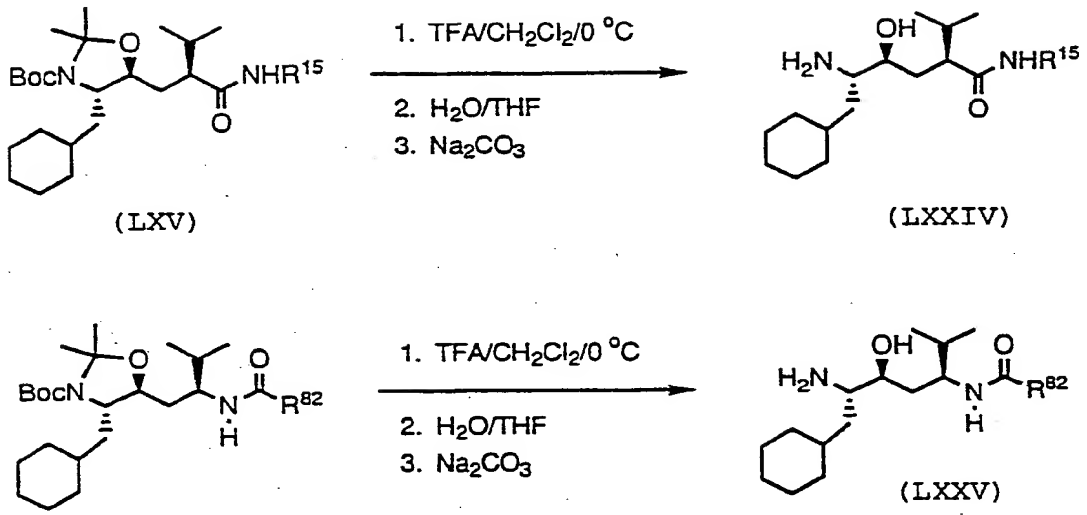


SCHEME XXA

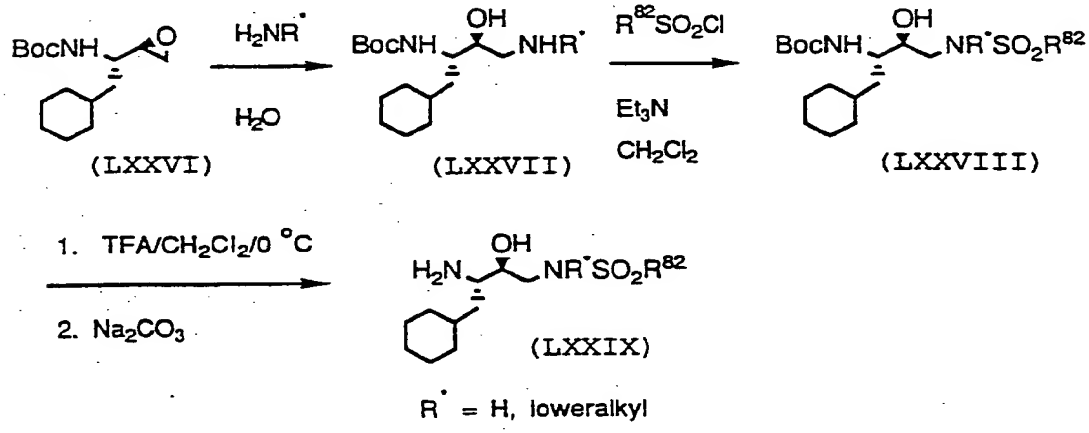


(LXIV) (LXX) (LXXI) (LXXII) (LXXIII)

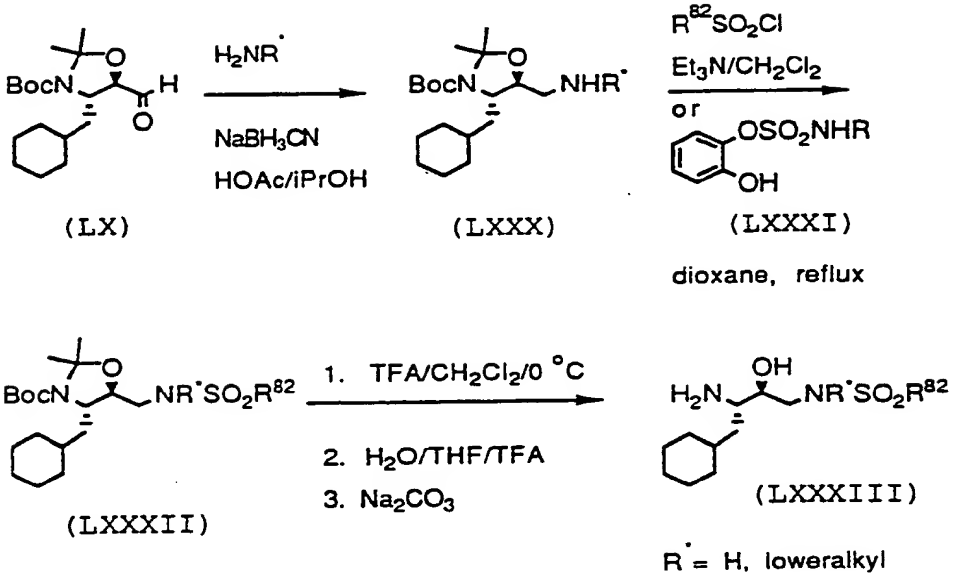
SCHEME XXI A



SCHEME XXII A



SCHEME XXIII A



(LX) (LXXX) (LXXXI)

(LXXXII) (LXXXIII)

R· = H, loweralkyl

In the above schemes, optically active or racemic starting materials can be used to obtain products of known or mixed stereochemistry.

Renin inhibitors having the general structure shown in group (10) can be made as shown in Schemes 1B-17B. The syntheses of segments containing substituents R_5 are described in the Examples or have previously been described (Kempf, et al., J. Med. Chem. 1987, 30, 1978; Luly, et al., J. Med. Chem. 1987, 30, 1609; Buhlmayer, et al., U.S. Patent No. 4,727,060; Morisawa, et al., European Patent

Application No. 0228192; Ten Brink, PCT Patent Application No. WO87/02986).

Scheme 1B discloses a general method for the synthesis of compounds of the invention containing substituted piperazines. The process involves reaction of the appropriately substituted piperazine with an alph-halo ester. The ester 2 is hydrolyzed ($LiOH/MeOH/H_2O$) and then coupled to the appropriately functionalized amine (in this case 2-amino-1-cyclohexyl-3,4-dihydroxy-6-methyl heptane) using a EDAC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, or other standard peptide coupling methods to provide the desired product 4.

Scheme 2B discloses a general method for the synthesis of compounds of the invention containing N-substituted benzyl piperazines. The dipeptide 5 is synthesized using a mixed anhydride coupling method. The diketopiperazine 6, which is formed by heating 5 in refluxing xylene, is reduced (excess lithium aluminum hydride (LAH) in THF) to give 7. Reaction of 7 with an alpha-bromo ester (in this case ethyl 2-bromo hexanoate) gives 8. The amine 8 is protected (Boc-anhydride in CH_2Cl_2) and then the ester is hydrolyzed ($LiOH/MeOH/H_2O$). The free acid 9 is then coupled to the hydrochloride salt of the appropriately functionalized amine (in this case 2-amino-1-cyclohexyl-3,4-dihydroxy-6-methyl heptane) using EDAC or other standard peptide coupling methods to provide 10.

Scheme 3B discloses a general method for the synthesis of benzyl ketopiperazine containing compounds of the invention. The reduced dipeptide 11 is synthesized by oxidation of the precursor protected amino alcohol, followed by a reductive amination. The free amine of 11 is

reacted with an alpha-bromo ester such as benzyl bromoacetate to give 12, which is deprotected by hydrogenolysis and then cyclized with EDAC-HOBT (hydroxybenzotriazole) or other peptide or lactam forming agents. The lactam-ester 13 is hydrolyzed ($LiOH/dioxane/H_2O$) and then coupled to the hydrochloride salt of the appropriately functionalized amine (in this case 2-amino-1-cyclohexyl-3,4-dihydroxy-6-methyl heptane) using a standard peptide coupling method such as EDAC to give the desired product 14.

Scheme 4B discloses a method for synthesizing substituted ketopiperazines of the invention which are isomeric with those prepared in Scheme 3. The methyl ester of D-Phe is protected with Boc-anhydride and then allylated with allyl bromide. The intermediate 15 is oxidized to aldehyde 16. Aldehyde 16 is coupled to an amino acid by reductive amination and then cyclized. The lactam-ester 18 is hydrolyzed (LiOH/water/dioxane) and then coupled to the hydrochloride salt of the appropriately functionalized amine (in this case 2-amino-1-cyclohexyl-3,4-dihydroxy-6-methyl heptane) to give the desired product 20.

Scheme 5B discloses the synthesis of compounds of the invention containing substitued delta-lactams. Valerolactone is alkylated (in this case with a benzyl group) by lithiation at -78°C in THF followed by an alkyl halide (benzyl bromide). The resulting lactone 21 is transesterified with benzyl alcohol. The primary alcohol 22 is oxidized using Swern conditions and then reductively aminated with an amino acid ester such as L-norleucine methyl ester. The benzyl ester 24 is subjected to hydrogenolysis to remove the benzyl group and the amino

acid is cyclized to give lactam 25 using EDAC or other standard peptide coupling or lactam forming methods. The lactam-ester is hydrolyzed and the acid is coupled to the hydrochloride salt of the appropriately functionalized amine (in this case 2-amino-1-cyclohexyl-3,4-dihydroxy-6-methyl heptane) to give the desired product 26.

Scheme 6B discloses a general method for synthesizing compounds of the invention containing amino substituted gamma- and delta-lactams. Compound 27 (J. AM. Chem. Soc. 79 5736 (1957)) is deprotonated and alkylated with allyl bromide to provide 28. Hydrolysis (aq. sodium hydroxide) followed by acidification provides the acid corresponding to 29, which is treated with excess ethereal diazomethane to provide 29. Oxidation of 29 gives aldehyde 30a. Reductive amination of 30a with the methyl ester of the desired amino acid hydrochloride salt (in this case His-OMe) provides the amino ester 31a, which is cyclized to the corresponding lactam 32 (n=1). The lactam ester 32 is hydrolyzed to the corresponding acid. The acid is coupled to the hydrochloride salt of the appropriately functionalized amine (in this case 2-amino-1-cyclohexyl-3,4-dihydroxy-6-methyl heptane) through a standard solultion phase peptide coupling method using a water soluble carbodiimide to give the desired product wherein n=1.

Hydroboration of 28 followed by oxidation gives the aldehyde 30b. Reductive amination of 30b with the methyl ester of the desired amino acid hydrochloride salt (in this case L-His-OMe) provides 31b. Lactam ester 32 (n=2) is produced by refluxing a methanolic solution of 31b with isopropyl amine. Ester hydrolysis, followed by coupling to

the hydrochloride salt of the appropriately functionalized amine (in this case 2-amino-1-cyclohexyl-3,4-dihydroxy-6-methyl heptane) using EDAC or other standard peptide coupling methods, provides the desired product wherein n=2.

Scheme 7B discloses a general method for synthesizing compounds of the invention containing an oxa-lactam. For example, D-phenylalanine is converted to D-3-phenyllactic acid 33, which is esterified to produce 34. The free hydroxy group is allylated with allyl bromide to provide ester 35, which is oxidized to the aldehyde 36. The aldehyde 36 is reductively aminated with the appropriate amino acid ester (in this case L-His-OMe) to give amino ester 37, which is thermally cyclized to lactam 38. Lactam ester 38 is hydrolyzed and the imidazole nitrogen is protected as the N-t-Boc derivative. The acid is then coupled to the hydrochloride salt of the appropriately functionalized amine (in this case 2-amino-1-cyclohexyl-3,4-dihydroxy-6-methyl heptane) using EDAC or other standard peptide coupling methods to produce the desired product 39.

Scheme 8B discloses a method for the synthesis of compounds of the invention containing an N-terminal substituted gamma-lactam. A mixed diester 40 is converted to acids 41 or 42, which are reduced to alcohols 43 or 44, respectively. Alcohols 43 and 44 are then oxidized to aldehydes 45 and 46. Reductive amination of 46 with the appropriate amino acid ester (in this case L-His-OMe di-p-toluenesulfonic acid salt) provides amino ester 48. This compound is converted to the free acid, which is then cyclized to 49. Similarly, reductive amination of 45 leads directly to the cyclic derivative 47. Protection of the

imidazole nitrogen of 47 and 49 as the N-t-Boc derivative, followed by ester hydrolysis, leads to acids 50 and 51. Amide formation with the hydrochloride salt of the appropriately functionalized amine (in this case 2-amino-1-cyclohexyl-3,4-dihydroxy-6-methyl heptane) using EDAC or other standard peptide coupling methods, followed by imidazole deprotection, affords 52 and 53, respectively.

Scheme 9B discloses a method for the synthesis of compounds of the invention containing an unsubstituted N-terminal cyclic urea. For example, Boc-phenylalanol 54 is oxidized to the aldehyde and reductively aminated with the appropriate amino acid ester (in this case L-His-OMe di-p-toluenesulfonic acid salt) to give mono-protected diamine 55. Removal of the protecting group and cyclization affords cyclic urea 56. Protection of the imidazole nitrogen and benzyl ester hydrogenolysis provides the acid 57. Amide formation with the hydrochloride salt of the appropriately functionalized amine (in this case 2-amino-1-cyclohexyl-3,4-dihydroxy-6-methyl heptane) using EDAC or other standard peptide coupling methods, followed by imidazole deprotection, affords 58.

Scheme 10B discloses a method for the synthesis of compounds of the invention containing an N'-substituted N-terminal cyclic urea. For example, phenylalanine methyl ester hydrochloride salt is reductively alkylated with an aldehyde or ketone (in this case isobutanal) and the resulting amine is protected to provide ester 60. The ester is reduced to the alcohol and the alcohol is oxidized to the aldehyde 61. Treatment of this aldehyde as described in Scheme 9 provides the desired compound 62.

Scheme 11B discloses a general method for the synthesis of benzyl ketopiperazine containing compounds which are isomeric with the compounds of Scheme 3. Alkylation and protection of amino-alcohol 63 provides alcohol 64. Oxidation and reductive amination of 64 gives diamine 65. Ring closure to 66, followed by coupling to the hydrochloride salt of the appropriately functionalized amine (in this case 2-amino-1-cyclohexyl-3,4-dihydroxy-6-methyl heptane) using EDAC or other standard peptide coupling methods to provide 67.

Scheme 12B discloses a general method for synthesizing compounds of the invention containing a sulfonyl substituted ketopiperazine. Compound 68 is sulfonylated, followed by ring formation, to give compounds such as 70 and 72. Deprotection and coupling of the resulting acid with the appropriately functionalized amine provides products such as 71 and 73.

Scheme 13B discloses a general method for synthesizing compounds of the invention containing amino substiuted delta-lactams. Compound 32 (Scheme 6, n=2) is treated with H_2 and Pd/C in acetic acid, followed by treatment with toluenesulfonyl chloride, to produce di-tosylate 75. Treatment of 75 with LiOH, followed by ditertbutyldicarbonate, produces acid 76. Acid 76 is coupled to the appropriately functionalized amine using EDAC, or other standard peptide coupling methods, to provide the desired product wherein n=2.

Scheme 14B discloses a general method for synthesizing compounds of the invention containing amino substituted delta-lactams which do not contain histidine residues. Compound 30b (Scheme 6, n=2) is reductively alkylated with

the corresponding amino acid methyl ester and the resulting product is thermally cyclized to delta-lactam 77. Treatment of 77 with HBr/HOAc, followed by reaction with sulfonyl chlorides or sulfamoyl chlorides, produces the amino protected compound 78. Ester hydrolysis of 78, followed by coupling to the appropriately functionalized amine using EDAC or other standard peptide coupling methods, provides the desired product wherein n=2.

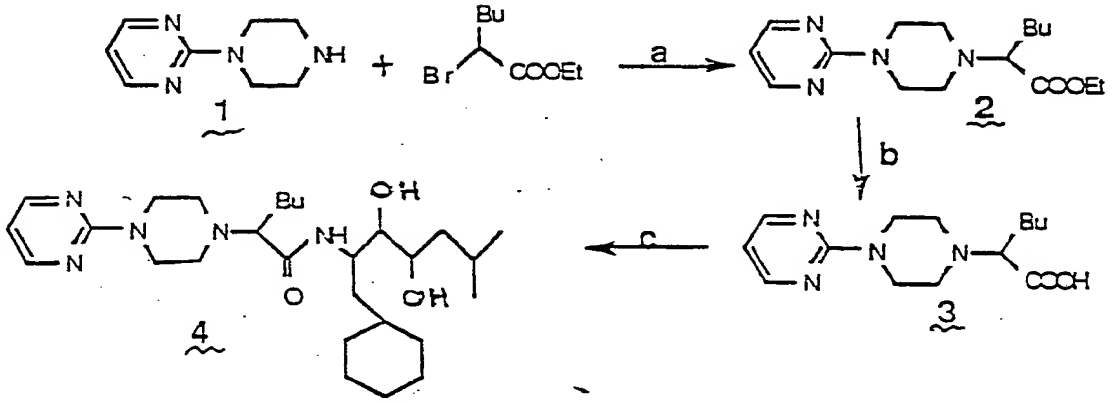
Scheme 15B describes an improved synthesis for the amine in Example 139. The lactone 82 was reduced with LAH at room temperature in 5 min and then cyclized under Mitsonobu condition to give the tetrahydrofuran derivative 84 in high yield. The free amine 85 was obtained by deprotection of 84 under acidic condition followed by a basic work-up with saturated $NaHCO_3$.

Scheme 16B discloses a general method for the synthesis of the compounds of the invention containing an N,N-disubstituted terminal amino group. Treatment of lactam ester 78 with various aldehydes and sodium cyanoborohydride in inert solvents produces the N-alkyl compound 79. Standard ester hydrolysis and coupling to various amines using standard peptide coupling methods produces the final inhibitors.

Scheme 17B discloses an improved method for the synthesis of lactam intermediates such as 32 and 77 which are used in the synthesis of compounds of the invention. Compound 86 (J. Chem. Soc. (c), 329, 1971) is deprotonated and alkylated with allyl bromide to provide 87. Hydrolysis (aq. lithium hydroxide followed by acidification) affords the amino acid which is treated with CBZ-NOS and then paraformaldehyde to give chiral oxazolidinone 88.

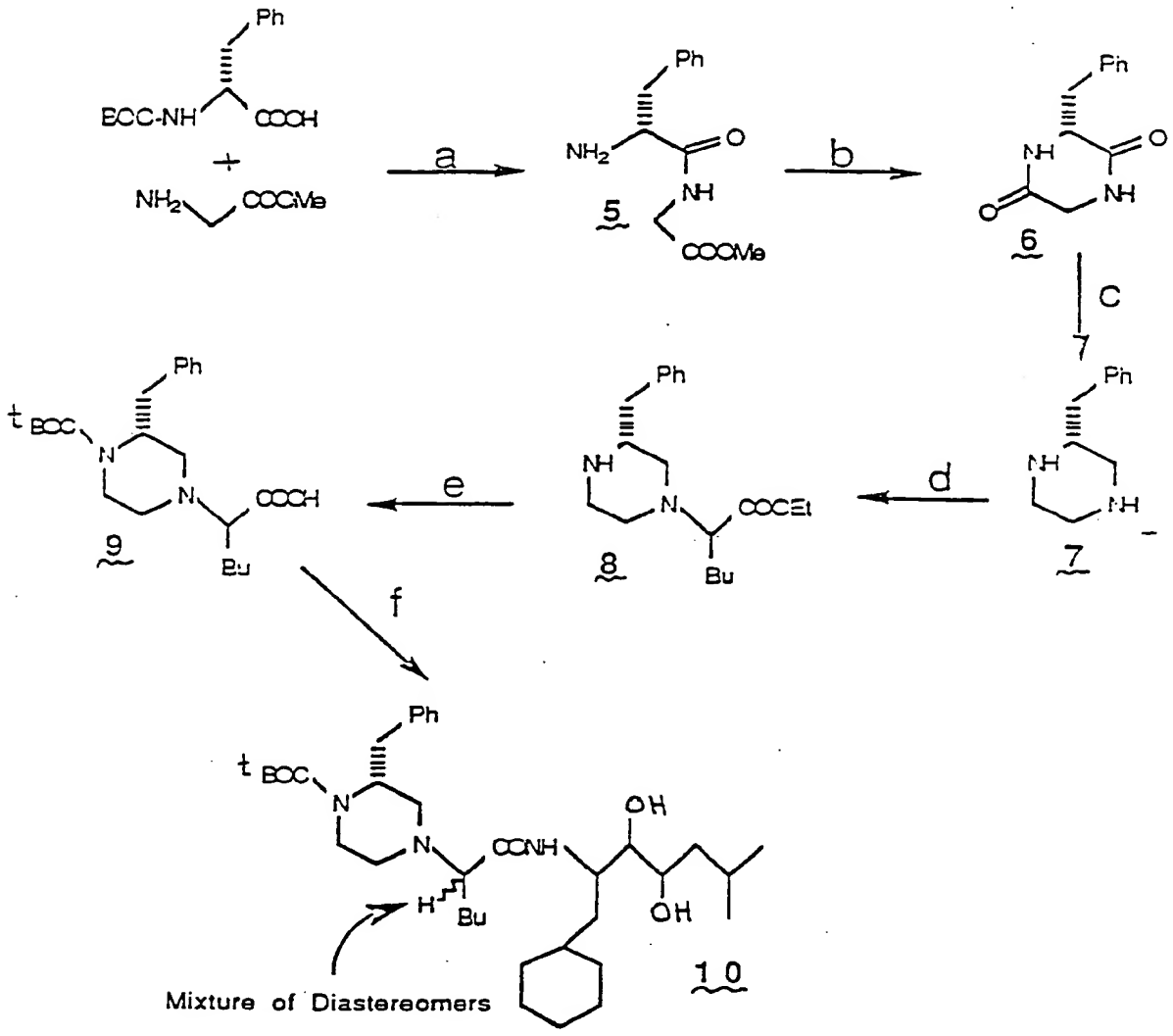
Hydroboration of 88 (9-BBN then NaOOH) and oxidation to the aldehyde (PCC) is followed by reductive alkylation with amino acid esters to provide the lactams.

Scheme-1 B



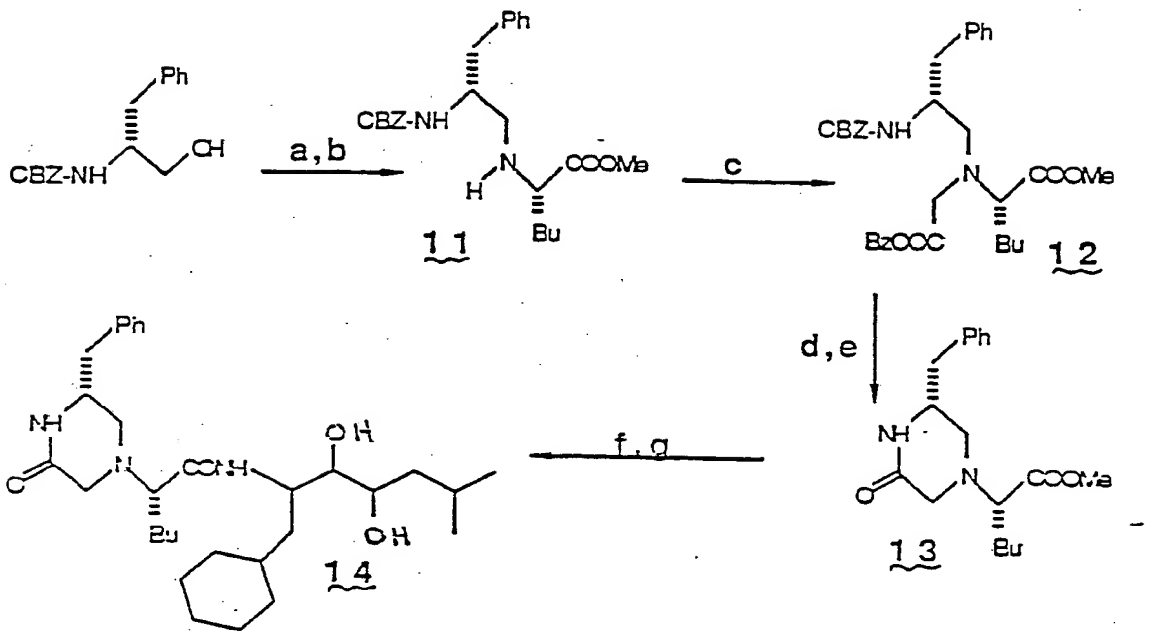
a: K_2CO_3, EtOH; b: LiOH, MeOH-H_2O; c: HOBT, EDAC, Amine.HCl

Scheme-2B



a: Mixed anhydride coupling followed by HCl/Dioxane
b: Heating in Xylene for 6 h
c: LAH in THF, Reflux overnight
d: Ethyl Bromohexanoate, K_2CO_3, Dioxane, Reflux for 2 h
e: ^tBOC-Anhydride, CH_2Cl_2
f: Hydrolysis followed by EDAC coupling of the amine

Scheme-3B



a: SO_3-Pyridine

b: nor-Leu-OMe, $NaCNBH_3$

c: Benzyl bromoacetate, Na_2CO_3, Dioxane

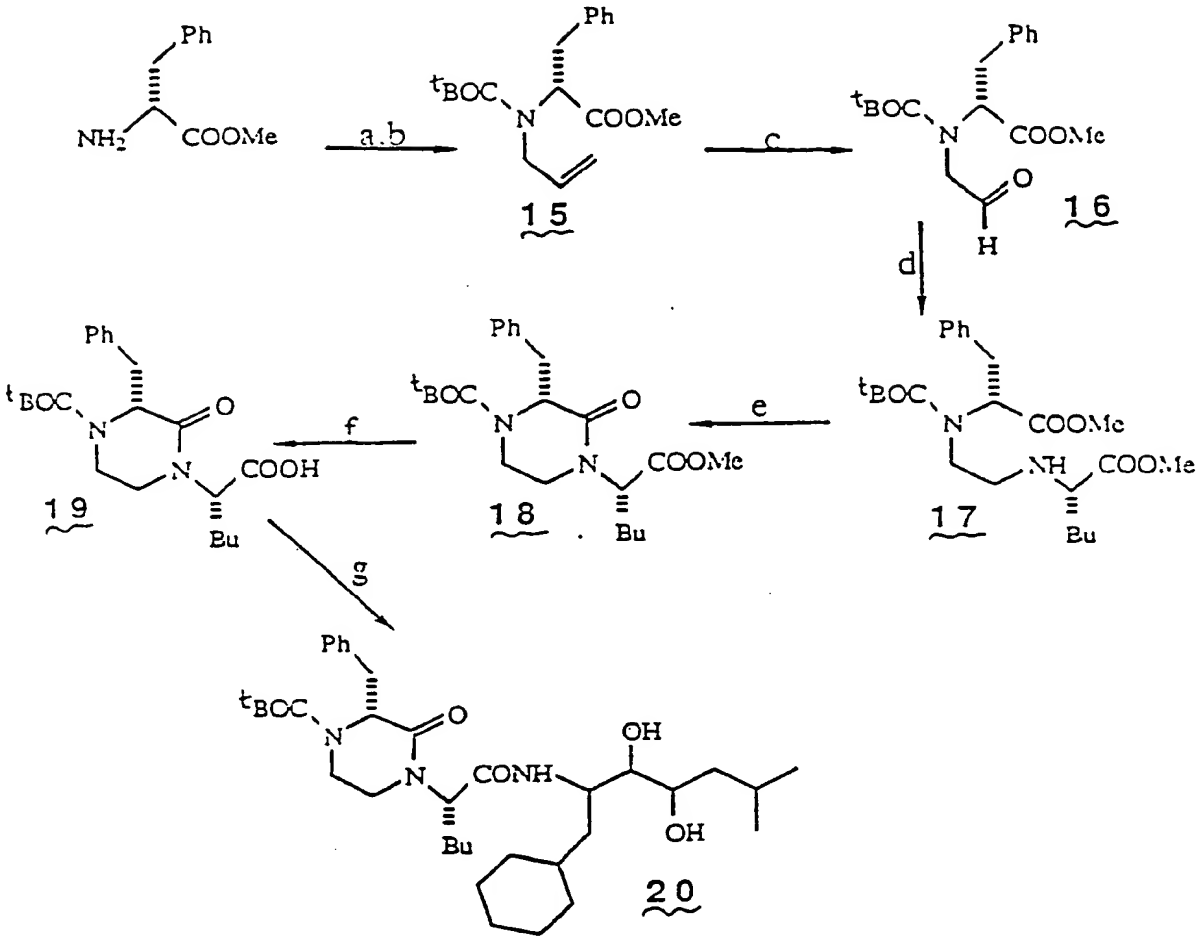
d: H_2-Pd, MeOH

e: EDAC, HOBT, DMF

f: LiOH, H_2O-Dioxane

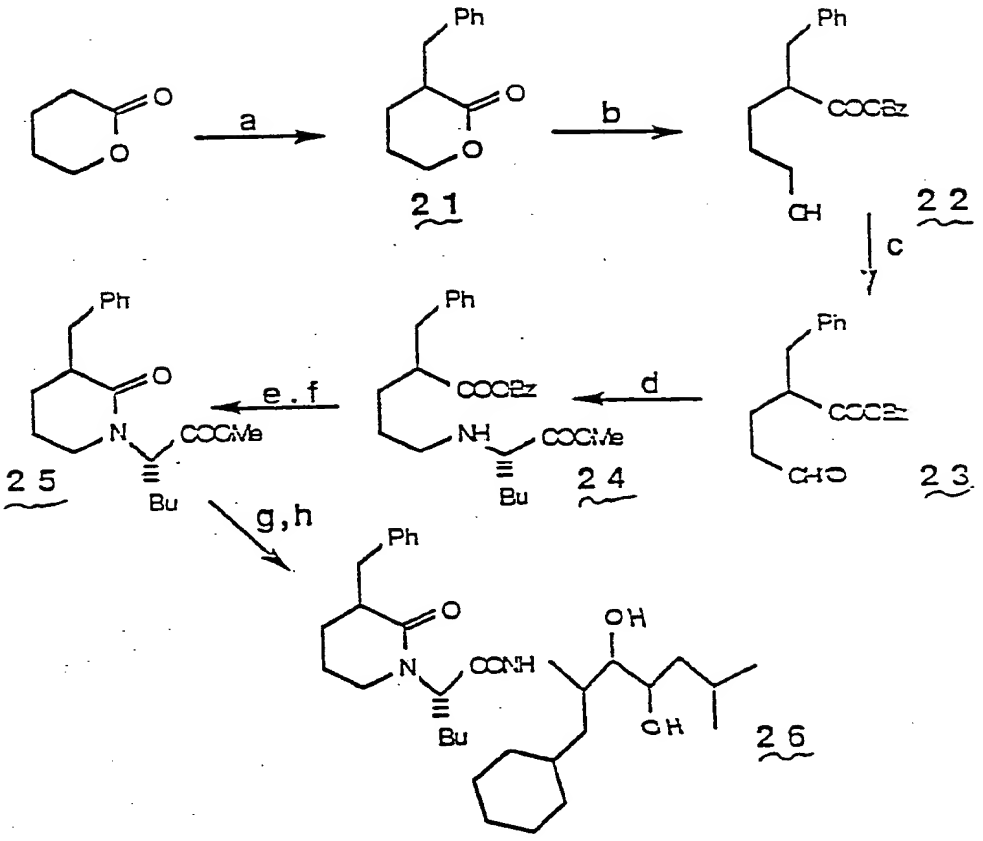
g: EDAC, HOBT, Amine.HCl, DMF

Scheme-4B



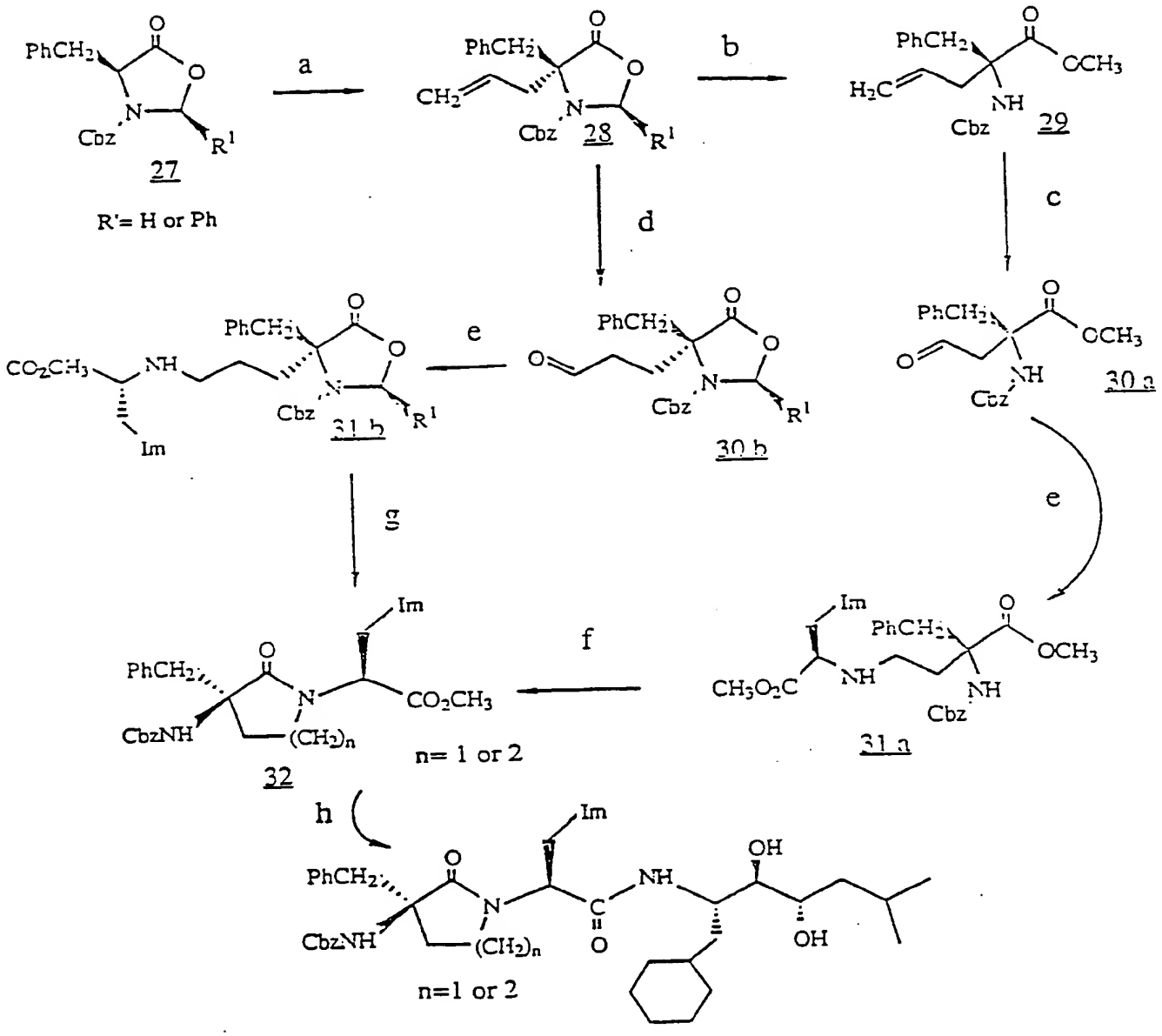
a: ^{t}BOC-Anhydride, CH_2CL_2
b: $NaN(TMS)_2$, Allyl Bromide, DMF
c: Ozone, CH_2Cl_2
d: nor-Leu-OMe, $NaCNBH_3$
e: Reflux in Xylene
f: LiOH, H_2O-Dioxane
g: EDAC, HOBT, Amine.HCl, DMF

Scheme-5B



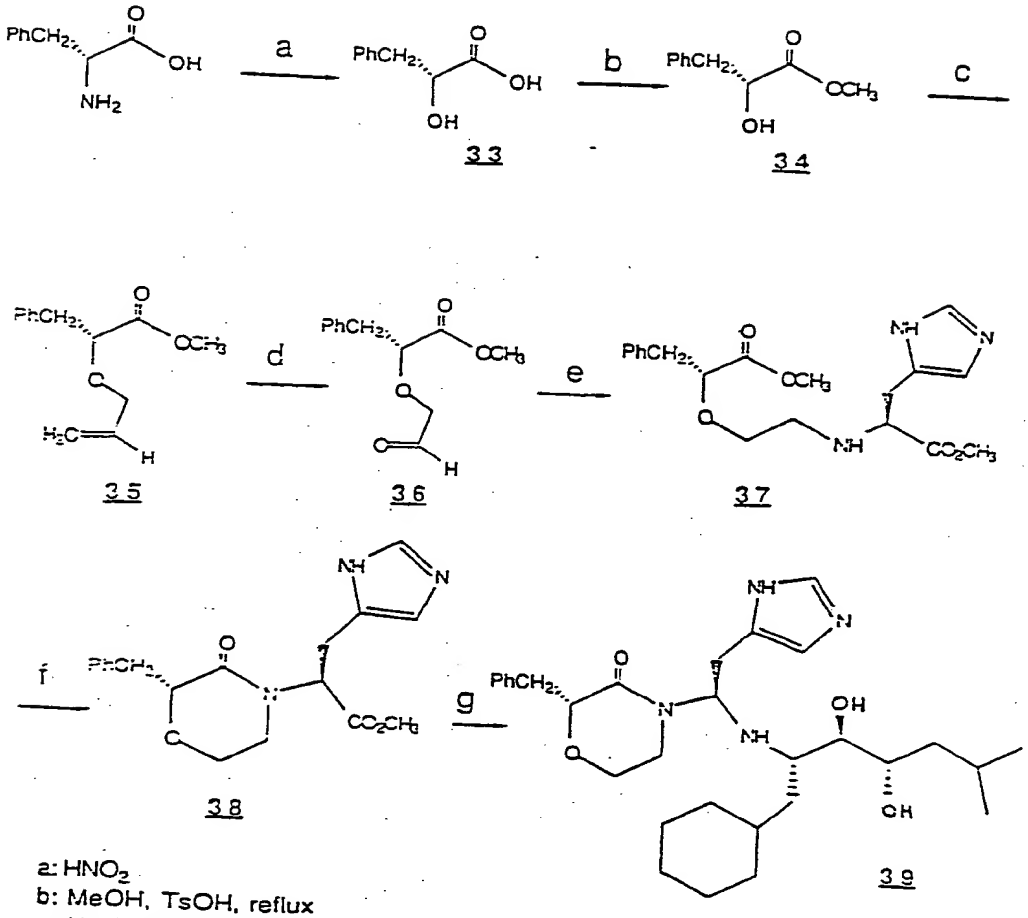
a: LDA, Benzyl Bromide, THF b: Methanol/Sulphuric Acid followed by Benzyl Alcohol/ TsOH , Reflux c: Oxalyl Chloride, DMSO,TEA d: L-nor-Leu-OMe, Sodium Cyanoborohydride IPA e: Hydrogen, 10% Pd-C, MeOH f: EDAC, HOBT,TEA,DMF g: LiOH, Diox-Water h: HCl.Amine, EDAC, HOBT, TEA, DMF

Scheme-6B



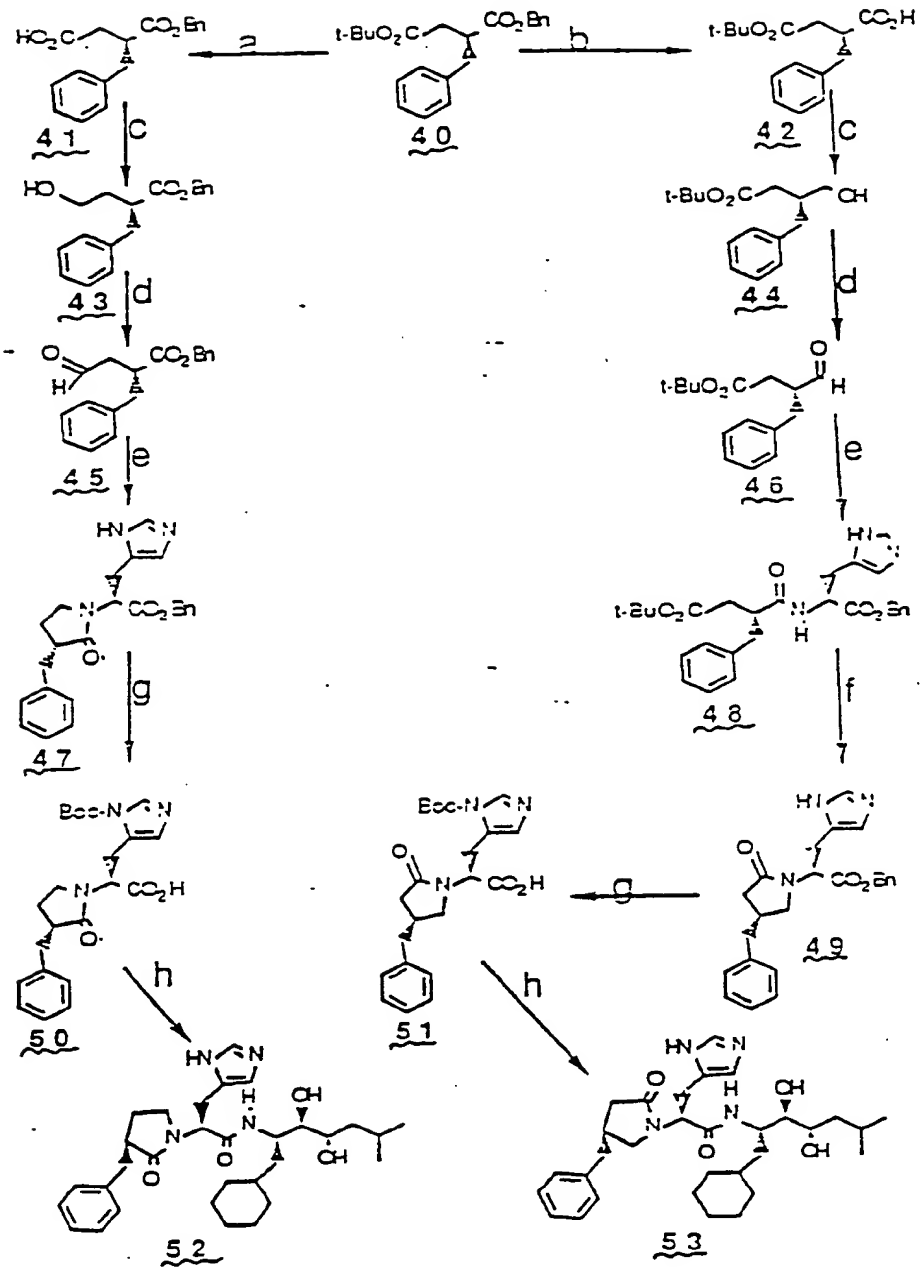
a: KHMDS,THF, -78°C,allyl bromide
b: aq. NaOH; H^+; CH_2N_2
c: O_3,-78°C,thenMe_2S
d: 9-BBN/THF,NaOOH;PCC
e: His-OMe,NaOAc,$NaCNBH_3$
f: HOBT,Toluene:DME,reflux
g: 2 eq. isopropylamine,MeOH, reflu
h: aq.LiOH:EDAC,Amine

Scheme-7B



a: HNO_2
b: MeOH, TsOH, reflux
c: NaH, DMF, allyl bromide
d: O_3, -78°C, Me_2S
e: His-OCH_3.NaOAc.$NaCNBH_3$
f: MeOH,reflux
g: LiOH, BocOBoc, amine, EDAC, HOAc

SCHEME 8B

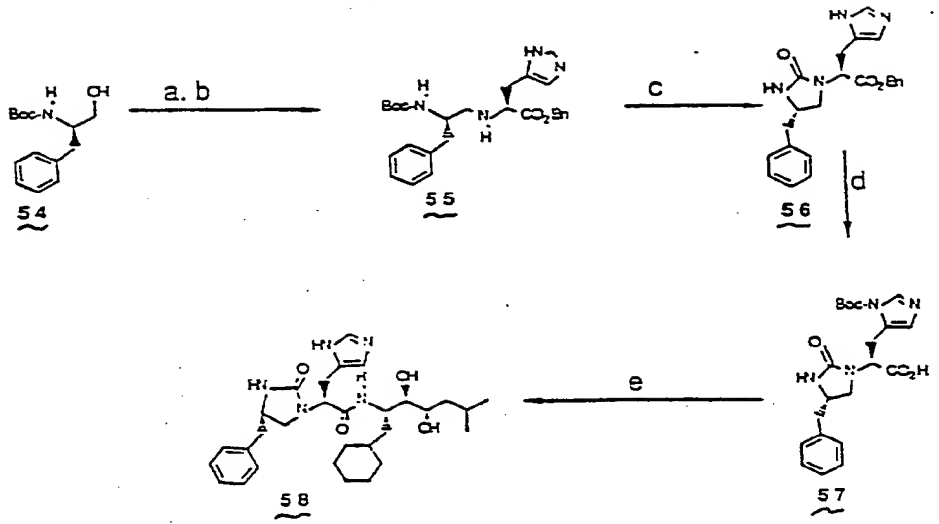


a: CF_3CO_2H; b: H_2, Pd/C; c: BH_3/THF; d: ClCOCOCl, DMSO, TEA;

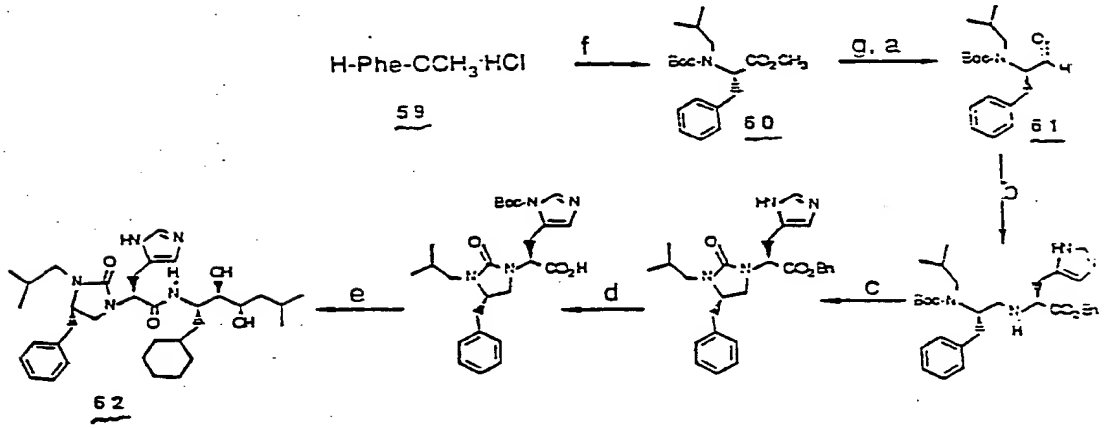
e: H-His-OBn·$TsOH_2$, NaOAc, $NaCNBH_3$; f: CF_3CO_2H, then EDAC, HOBT;

g: Boc-O-Boc, then H_2, Pd/C; h: EDAC, HOBT, Amine, then HOAc.

SCHEME 9B



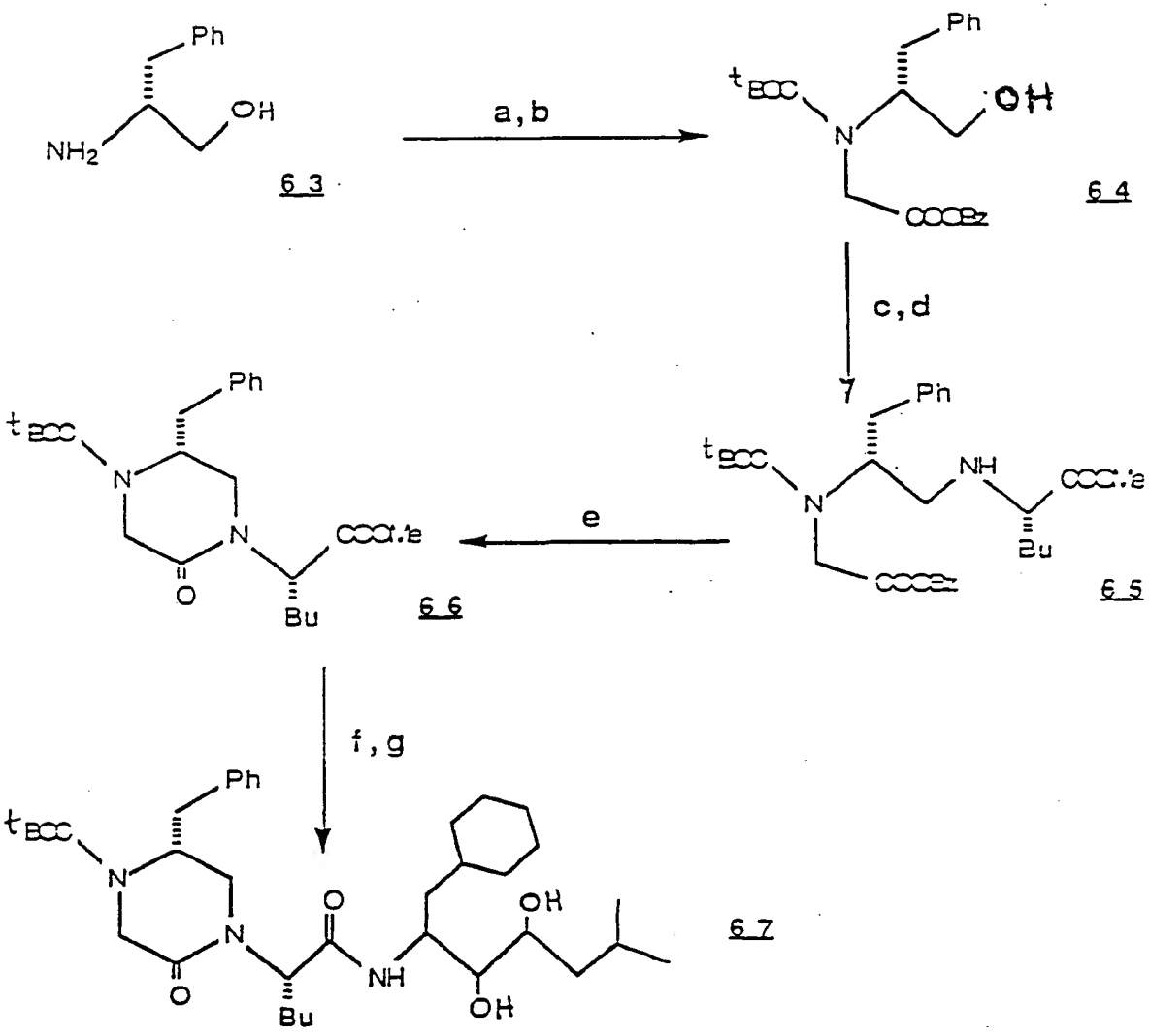
SCHEME 10B



a: ClCOCOCl, DMSO, TEA; b: H-His-OBn·$TsOH_2$, NaOAc, $NaCNBH_3$;

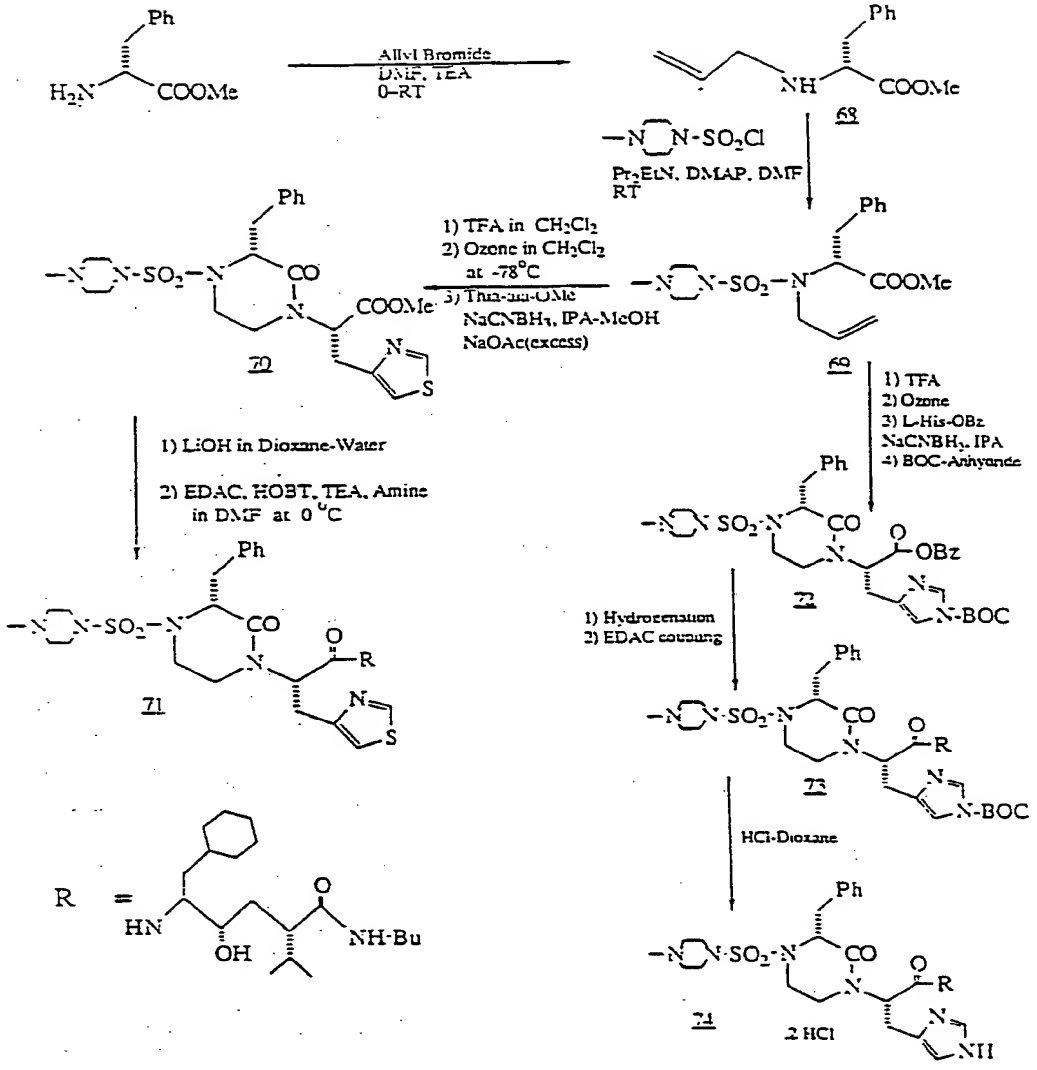
c: CF_3CO_2H, then CDI; d: Boc-O-Boc, then H_2, Pd/C; e: EDAC, HOST, Amine, then HOAc; f: $(CH_3)_2CHCHO$, NaOAC, $NaCNBH_3$, then Boc-O-Boc; g: $Ca(BH_4)_2$.

Scheme-11B

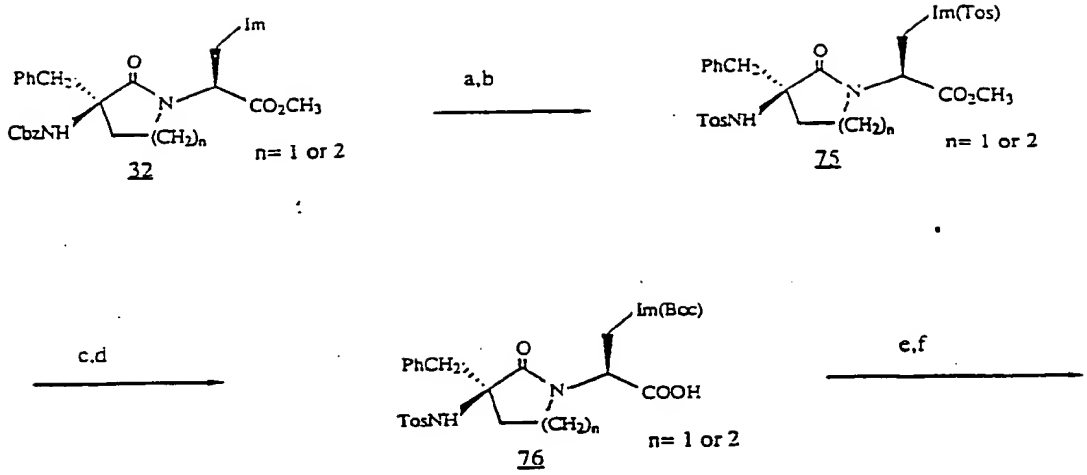


a) Benzyl bromoacetate, TEA, THF
b) BOC-Anhydride, Methylene Chloride
c) Pyridine-SO_3
d) L-nor-Leu-OMe, $NaCNBH_3$, IPA
e) Reflux in Xylene
f) NaOH, MeOH-H_2O
g) Amine, EDAC, HOBT, DMF, TEA

Scheme-12 B


Allyl Bromide
DMF, TEA
0-RT
68
Pr2EtN, DMAP, DMF
RT
1) TFA in CH2Cl2
2) Ozone in CH2Cl2
at -78°C
3) Thia-ala-OMe
NaCNBH3, IPA-MeOH
NaOAc(excess)
70
69
1) LiOH in Dioxane-Water
2) EDAC, HOBT, TEA, Amine
in DMF at 0 °C
1) TFA
2) Ozone
3) L-His-OBz
NaCNBH3, IPA
4) BOC-Anhyande
72
1) Hydrogenation
2) EDAC coupling
71
73
HCl-Dioxane
74
2 HCl
R =
HN
OH
NH-Bu

SCHEME 13B



a:H_2, Pd/C,HOAc

b:TsCl,NMM,DMAP,CH_2Cl_2

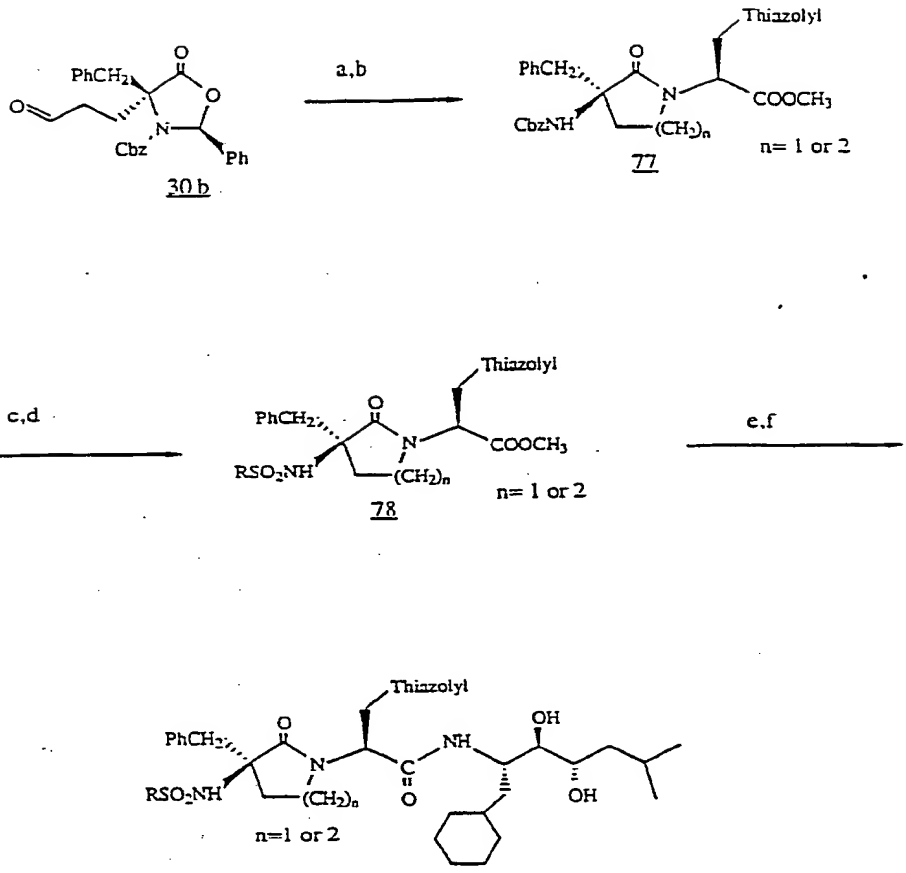
c:LiOH,H_2O

d:BocOBoc

e: Amine,EDAC, HOBT

f: HOAc,THF,H_2O

Scheme 14 B



a: Thiazolylalanine-OCH_3, $NaCNBH_3$, NaOAc

b: MeOH, NaOAc, Reflux

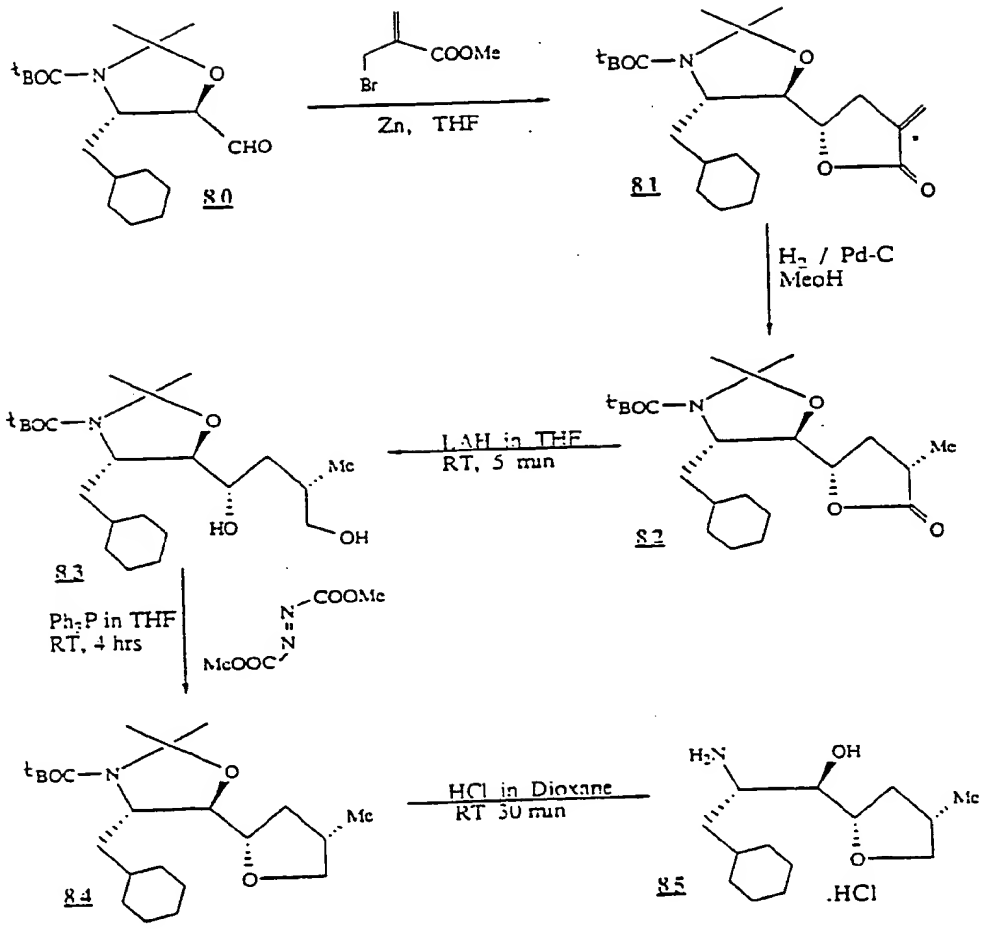
c: HBr / HOAc

d: RSO_2Cl,DMAP, NMM, DMF

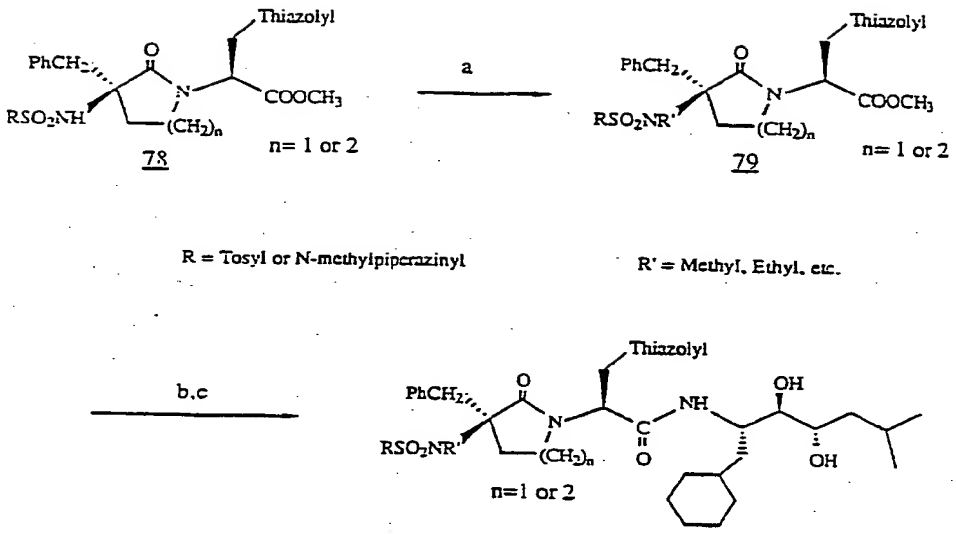
e: $LiOH.H_2O$

f: Amine,EDAC, HOBT

Scheme-15B


tBOC—N
O
CHO
80
COOMe
Br
Zn, THF
81
H2 / Pd-C
MeoH
LAH in THF
RT, 5 mun
82
Me
HO
OH
83
Ph3P in THF
RT, 4 hrs
MeOOC
COOMe
84
HCl in Dioxane
RT 30 mun
H2N
85
.HCl

SCHEME 16 B

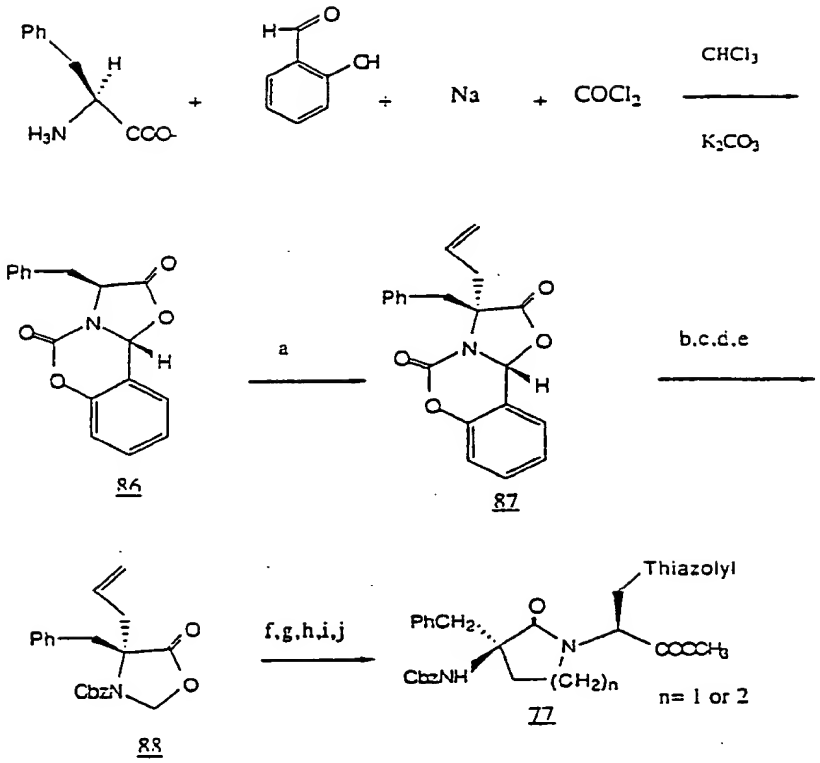


a: R'CHO, $NaCNBH_3$, CH_3CN

b: $LiOH,H_2O$

c: Amine, EDAC, HOBT

SCHEME 17 β



a: LiHMDS.DMPU.Allyl Bromide

b: $LiOH.H_2O$

c: 1N HCl

d: Cbz-Nos

e: HCHO, TsOH

f: 9-BBN

g: NaOOH

h: PCC

i: Thiala-OCH_3, $NaCNBH_3$

j: NaOAc.MeOH.Reflux

The following examples will serve to further illustrate preparation of the novel compounds of the invention.

Example 1

2(S)-(1(S)-(4-(Methoxymethoxy)piperidin-1-yl)carbonyl-2-phenyl)ethoxyhexanoic acid amide of 3-(4-morpholinyl)propyl 5(S)-amino-6-cyclohexyl-4(S)-hydroxy-2(S)-isopropylhexanamide

Example 1A: 4(S)-t-Butyloxycarbonylamino-5-cyclohexyl-3(R,S)-hydroxy-1-pentene

To a strired -78°C solution of Boc-cyclohexylalanine methyl ester (10.2 g, 35.8 mmol) in dry toluene (60 ml) was added diisobutylaluminum hydride (34 ml of a 1.5 M solution in toluene). After 30 min, vinyl magnesium bromide (108 ml of 1 M solution in tetrahydrofuran (THF)) was added. After stirring for 15 h at 0°C, the mixturte was carefully quenched with methanol, treated with Rochelle salts (22 ml of saturated aqueous solution in 140 ml H_2O), and filtered. After extracting the solids 5 times with ethyl acetate, the extracts and filtrate were combined and the organic phase was washed with brine, dried, filtered and evaporated to an oil (10.2 g). Chromatography on silica gel eluting with hexane/ethyl acetate mixtures provided 6.1 g of the desired product. Anal. calcd. for $C_{16}H_{29}NO_3$ .1/4 H_2O: C, 66.8; H, 10.3; N, 4.9.

Found: C, 66.9; H, 10.2; N, 4.7.

Example 1B: 3-(t-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-dimethyl-5-vinyloxazolidine.

The procedure of S. Thaisrivong (J. Med. Chem. **1987**, 30, 976) was employed. A solution of 40 g of the resultant compound of Example 1A and 102 g of 2-methoxypropene in 250 ml of dichloromethane was stirred at room temperature. Solid pyridinium p-toluenesulfonate (PPTS) (177 g) was added slowly to the reaction mixture. After addition was complete, the reaction was stirred for 1 h and neutralized by addition of solid sodium bicarbonate. The solids were filtered and the filtrate was concentrated. Flash chromatography on silica gel gave 57 g of the desired compound. IR ($CDCl_3$) 1690 (C=O carbamate) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.95 (m,1H), 5.32 (m,1H), 5.20 (dt,1H), 4.27 (dd,1H), 1.47 (s,9H).

Anal. Calcd. for $C_{19}H_{33}NO_3$: C, 70.55; H, 10.28; N, 4.33.

Found: C, 70.47; H, 10.27; N, 4.09.

Example 1C: 3-(t-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-dimethyloxazolidine-5-carboxaldehyde.

A solution of 10 g of the resultant compound of Example 1B in 150 ml of 2:1 dichloromethane: methanol was cooled in an dry-ice acetone bath. Ozone was bubbled through the solution until a blue color persisted (1 h). Dry nitrogen was then bubbled through the reaction mixture to remove excess dissolved ozone. The reaction mixture was cannulated into a suspension of 8 g zinc dust, 8 ml glacial acetic acid, 200 ml water, and 200 ml of methanol cooled to -45°C. After 5 min the bath was removed and the mixture allowed to warm to room temperature overnight. 100 ml of saturated sodium chloride was added and the

entire reaction mixture extracted with two 300 ml portions of dichloromethane. The combined dichloromethane extracts were decanted, dried ($MgSO_4$), filtered, and evaporated. The crude aldehyde was purified by flash chromatography (1:4) ethyl acetate:hexane to give 9.7 g of the desired compound as a mixture of diastereomers (3:1 trans:cis) as judged by the integrated resonances of the two aldehyde protons. IR ($CDCl_3$) 1735 (C=O aldehyde), 1690 (C=O carbamate) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.83 (s,1H,CHO), 9.73 (d,1H,CHO cis diastereomer), 4.14 (m,1H), 1.46 (s,9H).

Anal. Calcd. for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N, 4.30.

Found: C, 65.27; H, 9.79; N, 4.20.

Equilibration of Aldehyde Isomers

A suspension of 25 g of the above aldehyde in 300 ml of methanol and powdered potassium carbonate (10.7 g) was stirred at room temperature for 6 h. The reaction mixture was cooled in an ice-water bath and treated with 9.3 g of glacial acetic acid for 5 min. A solution of 0.5 M sodium dihydrogen phosphate (300 ml) was added to the mixture. After 30 min, the solution was concentrated to one-half the volume under reduced pressure and extracted with ether (600 ml). The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated. The aldehyde was purified by flash chromatography using (1:4) ethyl acetate:hexane to give 19.5 g of the desired compound as an 8:1 mixture of trans:cis diastereomers.

Example 1D: 3-(3(R)-(3-(tert-Butyloxycarbonyl)-2,2-dimethyl-4(S)-cyclohexylmethyl-5(R)-oxazolidinyl)-3-hydroxy-2(R)-isopropyl-1-oxopropyl)-4(R)-methyl-5(S)-phenyl-2-oxazolidinone.

The title compound was prepared in analogy to the procedure of S. Thaisrivongs, D. T. Pals, L. T. Kroll, S. R. Turner and F. S. Han, *J. Med. Chem.* **1987**, *30*, 976-82, from the resultant compound of Example 1C, in 63% yield. M. p. 97 °C. ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 3H), 1.06 (d, 3H), 1.1 (d, 3H), 1.48 (s, 9H), 0.9-1.9 (several bm, 12 H total), 2.12 (bd, 1H), 2.3 (m, 1H), 3.81 (dd, 1H), 3.94 (td, 1H), 4.04 (bm, 1H), 4.22 (dd, 1H), 4.84 (dq, 1H), 5.61 (d, 1H), 7.31-7.45 (m, 5H). High resolution mass spectrum. Calcd. for $(M+H)^+$ of $C_{33}H_{51}N_2O_7$: 587.3698. Found: 587.3696.

Analysis. Calcd. for $C_{33}H_{50}N_2O_7$: C, 67.55; H, 8.59; N, 4.77. Found: C, 67.41; H, 8.61; N, 4.77.

Example 1E: 3-(3(R)-(3-(tert-Butyloxycarbonyl)-2,2-dimethyl-4(S)-cyclohexylmethyl-5(R)-oxazolidinyl)-3-((1-imidazolyl)thionyloxy)-2(R)-isopropyl-1-oxopropyl)-4(R)-methyl-5(S)-phenyl-2-oxazolidinone.

The resultant compound from Example 1D (1.840 g, 3.136 mmol) and 1,1'-thiocarbonyldiimidazolide (1.128 g, 6.330 mmol) were refluxed in 8 mL dry 1,2-dichloroethane under a nitrogen atmosphere for 24 h. The mixture was concentrated and the residue purified by flash chromatography (2.5% MeOH-CH_2Cl_2) to afford 1.896 g (87%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3H), 1.04 (d, 3H), 1.08 (d, 3H), 1.5 (bs, 9H), 0.9-1.9 (several bm, 13H total), 2.05 (m, 1H), 4.13 (bm, 1H), 4.23 (dd, 1H), 4.81 (dd, 1H), 4.94 (dq, 1H), 5.70 (d, 1H), 6.33 (dd, 1H), 7.06 (bs, 1H), 7.3-7.5 (m, 5H), 7.61 (bs, 1H), 8.40

(bs, 1H). High resolution mass spectrum. Calcd. for $(M+H)^+$ of $C_{37}H_{53}N_4O_7S$: 697.3635. Found: 697.3629.

Analysis. Calcd. for $C_{37}H_{52}N_4O_7S$: C, 63.77; H, 7.52; N, 8.04. Found: C, 63.58; H, 7.44; N, 7.94.

Example 1F: 3-(3-(3-(tert-Butyloxycarbonyl)-2,2-dimethyl-4(S)-cyclohexylmethyl-5(S)-oxazolidinyl)-2(R)-isopropyl-1-oxopropyl)-4(R)-methyl-5(S)-phenyl-2-oxazolidinone.

A solution of the resultant product from Example 1E (6.50 g, 9.33 mmol) in 275 ml of dry toluene was degassed with argon for 30 min, then warmed to reflux (under argon). A solution of tri-n-butyltin hydride (5.43 g, 18.6 mmol) in 75 ml of dry, degassed toluene was added dropwise over 15 min. After an additional 2 h of reflux, the reaction was cooled, concentrated and purified by flash chromatography (5% EtOAc-hexanes) to afford 4.82 g (90%) of the title compound as a white foam. ^1H NMR ($CDCl_3$) δ 0.90 (d, 3H), 0.92 (d, 3H), 0.9-1.1 (bm, 3H), 1.06 (d, 3H), 1.15-1.35 (bm, 3H), 1.51 (s, 9H), 1.57-2.14 (several bm, 16H total), 3.84 (m, 1H), 3.97 (m, 1H), 4.85 (dq, 1H), 5.68 (d, 1H), 7.3-7.46 (m, 5H). Mass spectrum: $(M+H)^+ = 571$.

Analysis. Calcd. for $C_{33}H_{50}N_2O_6$: C, 69.44; H, 8.83; N, 4.91. Found: C, 69.31; H, 8.82; N, 4.89.

Example 1G: 2(S)-((3-(tert-Butyloxycarbonyl-2,2-dimethyl-4(S)-cyclohexylmethyl-5(S)-oxazolidinyl)methyl)-3-methylbutanoic acid.

Using the procedure of D. A. Evans, T. C. Britton and J. A. Ellman, *Tetrahedron Lett.* **1987**, *28*(49), 6141-44, the resultant product from Example 1F (6.10 g, 10.7 mmol) was

hydrolyzed with aq. LiOH and hydrogen peroxide in THF. The crude material was purified by flash chromatography (15% EtOAc-0.5% HOAc-hexanes) to provide 3.53 g (90%) of the title compound as a viscous colorless oil. ^1H NMR ($CDCl_3$) δ 0.96 (d, 3H), 1.00 (d, 3H), 1.1-1.3 (bm, 5H), 1.48 (s, 9H), 1.5-1.9 (several bm, 15H total), 2.0 (m, 1H), 2.66 (m, 1H), 3.7 (bm, 1H), 3.90 (m, 1H). Mass spectrum: $(M+H)^+ = 412$.

Analysis. Calcd. for $C_{23}H_{41}NO_5 \cdot 0.25\ H_2O$: C, 66.39; H, 10.05; N, 3.37. Found: C, 66.46; H, 9.84; N, 3.36.

Example 1H: 3-(4-Morpholinyl)propyl 2(S)-((3-(tert-butyloxycarbonyl)-2,2-dimethyl-4(S)-cyclohexylmethyl-5(S)-oxazolidinyl)methyl)-3-methylbutanamide.

The procedure of P. Buhlmayer, et. al., *J. Med. Chem.* **1988**, *31*(9), 1839-46 is adapted. The resultant compound from Example 1G (75 mg, 0.182 mmol), HOBt (42.0 mg, 0.274 mmol) and N-methylmorpholine (55 mg, 0.55 mmol) were dissolved in 1.0 ml dry DMF, and the solution was cooled to -20 °C (under nitrogen). EDAC (53 mg, 0.28 mmol) was added as a solid, and the resulting mixture was stirred at -20 to 0 °C for 1 h. The mixture was sealed, and allowed to react at 0 °C (in refrigerator) for 48 h. To the resulting solution was added 4-(3-aminopropyl)morpholine (0.23 mmol). The resulting solution was stirred at 0 °C for 4 h, and for a further 20 h, allowing it to warm slowly to room temperature. The volatiles were removed by high vacuum distillation, and the residue was partitioned between CH_2Cl_2 and aq. $NaHCO_3$. The aqueous phase was extracted 3X with CH_2Cl_2, and the combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography (4% MeOH-CH_2Cl_2) provided the desired compound.

^{1}H NMR ($CDCl_3$) δ 0.92 (d, 3H), 0.95 (d, 3H), 1.46 (s) and 1.48 (s, 12H total), 1.57 (bs, 3H), 0.8-1.8 (several bm, 18H total), 2.01 (m, 1H), 2.46 (bm, 6H), 3.37 (m, 2H), 3.64 (bm, 1H), 3.75 (bm, 5H), 6.80 (bt, 1H). High resolution mass spectrum. Calcd. for $(M+H)^+$ of $C_{30}H_{56}N_3O_5$: 538.4220. Found: 538.4220.

Example 1I: 1(S)-(4-(Methoxymethoxyl)piperidin-1-yl-carbonyl)-2-phenylethanol.

A solution of 176 g (1.3 mol) of 1-hydroxybenzotriazole (Aldrich), 80 g (0.48 mol) of L-3-phenyllactic acid (prepared from L-phenylalanine) 76 g (0.52 mol) of 4-(methoxymethoxy)piperidine in 800 mL of DMF was cooled to -25 0°C (internal temperature) while 132 g EDC HCl (Saber Labs) was added (mechanical stirring). After addition the reaction was stirred to rt over 24 h. Excess DMF was removed under high vacuum and the residue dissolved into 1.5 L of ethyl acetate. The ethyl acetate solution was washed with 4 L of saturated sodium bicarbonate. The ethyl acetate layer was separated, dried ($MgSO_4$) and evaporated to give approximately 138 g of crude amide. The product was isolated by silica gel chromatography using ethyl acetate/hexane as eluant. Yield 120 g (79%).

^{1}H NMR ($CDCl_3$, TMS) δ 1.61 (m,2H), 1.81 (m,2H), 2.89 (m,2H), 3.38 (s,3H), 3.5 (m,2H), 3.79 (m,2H), 3.96 (m,1H), 4.62 (t,1H), 4.68 (s,2H).

Example 1J: 2(S)-(1(S)-(4-(Methoxymethoxy)piperidin-1-yl-carbonyl)-2-phenylethoxy)hexanoic acid.

The resultant compound of Example 1I (1.45 g, 4.95 mmol), in 10 ml THF was added dropwise to the cooled suspension of sodium hydride (60% dispersion in oil, 0.5 g, 11.2 mmol) in 4 ml THF (0-5oC). The suspension was

stirred for 20 mins at 0-5oC and then warmed up to room temperature and stirred for additional 1 h. Solution of D-2-bromohexanoic acid in 6 ml THF was added dropwise to the cooled suspension (0-5oC) at N_2 atmosphere. It was then allowed to warm up to room temperature and stirred overnight. Quenched with cold H_2O and extracted with ethylacetate to remove undesired starting material. It was acidified with 1 M sodium hydrogen sulfate and extracted with chloroform. After filtration and evaporation, the crude product was purified on silica gel, eluted with CH_2Cl_2: CH_3OH: AcOH (19.4 = 0.3:0.3) to obtain 0.79 g of desired acid (43 % yield).

^1H NMR ($CDCl_3$, TMS) δ 0.88 (t,3H), 3.35 (s,3H), 3.98 (bt,1H), 4.6 (m,1H), 4.64 (s,2H), 7.38 (m,5H). Mass spectrum: $(M+H)^+ = 408$.

Example 1K: 2(S)-(1(S)-(4-(Methoxymethoxy)piperidin-1-yl)carbonyl-2-phenyl)ethoxyhexanoic acid amide of 3-(4-morpholinyl)propyl 5(S)-amino-6-cyclohexyl-4(S)-hydroxy-2(S)-isopropylhexanamide.

The resultant compound from Example 1H (0.161 mmol) was deprotected by dissolving in 1.0 ml dry CH_2Cl_2, cooling the solution to -10 °C (under nitrogen), and treating with 1.0 ml of trifluoroacetic acid. The resulting solution was stirred at -10 to 0 °C for 4 h. The solvents were largely removed with a stream of nitrogen, and the residue (as a concentrated solution in trifluoroacetic acid) was dissolved in 1.0 ml THF and 0.3 ml water at 0 °C. The solution was allowed to warm slowly to ambient temperature over 18 h. The crude aminoalcohol was isolated by basifying the reaction with an excess of 1.0 M aq. Na_2CO_3, saturating the solution with NaCl, and

extracting with 5 x 10 ml of 5% EtOH-$CHCl_3$. The combined organic phases were washed with brine, dried (Na_2SO_4), concentrated, and the residue placed under high vacuum overnight to yield 66.2 mg (>100%) of yellow viscous oil.

Coupling was acheived by combining the resultant compound from Example 1J (72 mg, 0.177 mmol), the above aminoalcohol (0.168 mmol), HOBt (34 mg, 0.22 mmol) and N-methylmorpholine (25 mg, 0.25 mmol) in 1.0 ml dry DMF. The resulting solution was cooled to -20 °C (under argon), and EDAC (45 mg, 0.23 mmol) was added. The reaction was allowed to slowly warm to room temperature as the ice bath melted, for a total of 24 h. The solvent was removed by high vacuum distillation, and the residue was partitioned between 15 ml CH_2Cl_2, 9 ml sat. aq. $NaHCO_3$ and 1 ml H_2O. The aqueous phase was further extracted (3 X 10 ml CH_2Cl_2), and the combined organic phases were washed with 10 ml brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography yielded the title compound as a hygroscopic glassy solid, m.p. 49-51 °C. ^1H NMR ($CDCl_3$) δ 0.90 (m), 0.91 (d) and 0.92 (d, 9H total), 0.65-1.90 (several bm, approx. 28H total), 2.02 (m, 1H), 2.45 (bm, 6H), 2.95 (m, 1H), 3.05 (dd, 1H), 3.20 (bm, 2H), 3.36 (s, 3H), 3.45 (m, 2H), 3.6-4.0 (several bm) and 3.71 (m, 10H total), 4.48 (dd, 1H), 4.68 (s, 2H), 5.80 (d) and 5.88 (d, 1H total), 6.87 (bt, 1H), 7.3 (bm, 5H). Mass spectrum: $(M+H)^+ = 787$.

Example 2

(2S)-((3S)-((N-methylpiperazinsulfonyl) amino-3-phenylmethyl-2-oxo-1-piperidinyl)-3-(4-thiazolyl)propionic acid amide of (2S,4S,1'R,2'S)-2-(2'-amino-3'-cyclohexyl-1'-hydroxypropyl)-4-methyltetrahydrofuran

Example 2A: (2S,4S)-3-Benzyloxycarbonyl-2-phenyl-4-phenylmethyl-5-oxo-oxazolidine

Following the procedure of Karady, Tett. Lett. 25 4337 (1984), N-Cbz-L-phenylalanine (25 g, 83.5 mmol), benzaldehyde (18 g, 170 mmol) and p-toluenesulfonic acid (11.2 g, 58 mmol) were suspended in 1,1,1-trichloroethane (300 ml). The solution was refluxed for 18 hr and the water was removed by azeotropic distillation using a Dean-Stark trap for liquids heavier than water. After cooling, the reaction was washed with saturated aqueous $NaHCO_3$ (3x50 ml), water (1x50 ml), dried over sodium sulfate and concentrated in vacuo to produce an orange oil. After about 1 hr, a solid crystallized from the oil and it was collected by vacuum filtration. The orange solid was recrystallized from ethyl acetate/hexane to produce colorless crystals (4.0 g, 12%); mp 120-122°C. MS (CI): 405 $(M+NH_4)^+$, 388 $(M+H)^+$.

Example 2B: (2S,4S)-3-Benzyloxycarbonyl-2-phenyl-4-phenylmethyl-4-(1-(2-propenyl))-5-oxo-oxazolidine

A 250 ml round-bottom flask was charged with the resultant compound from Example 2A (3.75 g, 9.7 mmol), THF

(100 ml) and a magnetic stir bar. While under a nitrogen atmosphere, the flask was cooled to -78°C and via a syringe potassium hexamethyldisilylamide (25 ml, 12.5 mmol, 0.5 M solution in toluene) was added dropwise. After 15 min at -78°C, allyl bromide (1.76 g, 14.6 mmol, passed through neutral alumina prior to addition) was added over 1 min. After 1.5 h, the reaction was quenched with saturated aqueous NH_4Cl (100 ml) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3x100 ml) and the combined oraginc extracts were washed with saturated aqueous NaCl (2x50 ml), dried over Na_2SO_4 and concentrated in vacuo to afford a light yellow oil (4.4 g). Flash chromatography (100 g silica gel, 20% ethyl acetate/hexane, 8 ml fractions) afforded the desired product. mp 102-104°C. MS (DCI): 445 $(M+NH_4)^+$, 428 $(M+H)^+$.

Example 2C: (2S,4S)-3-Benzyloxycarbonyl-2-phenyl-4-phenylmethyl-4-(1-(3-hydroxypropyl))-5-oxo-oxazolidine

The resultant compound of Example 2B (3 g, 7 mmol) was dissoved in dry THF (100 ml) and then treated with 9-BBN (0.5 M in THF, 21 ml, 10.5 mmol). After stirring overnight at room temperature, excess 9-BBN was quenched by the dropwise addition of water (1 ml). The reactoin flask was then immersed in a room temperture water bath, followed by the concurrent and dropwise addition of 3 N NaOH (23 ml, 69 mmol) and 30% H_2O_2 (23 ml). Stirring was continued for 10 min after the addition was completed, after which the solution was staurated with solid NaCl. The layers were separated and the aqueous layer was

extracted with ether (3x50 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2x50 ml), dried over Na_2SO_4 and concentrated in vacuo to afford a colorless solid. Flash chromatography (100 g silica gel, 40% ethyl acetate/hexane) afforded the title compound as a colorless solid. Recrystallization from methylene chloride/hexane provided the title compound as colorless crystals. mp 130-131°C. MS (DCI): 463 $(M+NH_4)^+$, 446 $(M+H)^+$.

Example 2D: (2S,4S)-3-Benzyloxycarbonyl-2-phenyl-4-phenylmethyl-4-(2-(ethylcarboxaldehyde))-5-oxo-oxazolidine

The resultant compound from Example 2C (860 mg, 1.9 mmol) was dissoved in methylene chloride (10 ml) and added to a vigorously stirred mixture of PCC (1.0 g, 4.9 mmol) and 4 A molecular sieves (4 g) in methylene chloride (100 ml). Additional portions of PCC (0.5 g, 2.5 mmol) were added after 30 min and 45 min. After 1 h total reaction time, the mixture was poured into moist ether (200 ml). The reaction flask was rinsed with ether (4x50 ml) and the combined organic solutions were filtered through celite and concentrated in vacuo to afford a dark semisolid. The crude product was dissoved in methylene chloride and fltered through a 4 inch column of florisil. The filtrate (200 ml) was concentrated in vacuo to afford the title compound as a light yellow oil (450 mg, 52%). MS (DCI): 461 $(M+NH_4)^+$, 444 $(M+H)^+$.

Example 2E: (2S)-Methyl-((3S)-((Benzyloxycarbonyl) amino-3-phenylmethyl-2-oxo-1-piperidinyl)-3-(4-thiazolyl)propionate

To the resulting aldehyde of Example 2D (1 g, 2.2 mmol) in isopropanol (40 ml) as added the bis hydrochloride salt of (L)-(4-thiazolyl)alanine (620 mg, 2.4 mmol), anhydrous sodium acetate (6.3 mmol) and sodium cyanoborohydride (3.18 mmol). After 80 h at room temperature, the mixture was poured into sturated $NaHCO_3$ solution and extracted wilth ethyl acetate which was dried over Na_2SO_4 and evaporated.

The resulting compound was treated with anhydrous sodium acetate (22 mmol) and glacial acetic acid (5 drops) in dry MeOH (30 ml). After heating for 72 h at 110°C in a sealed tube, the solution was concentrated in vacuo and the resulting residue was partitioned between ethyl acetate and saturated $NaHCO_3$. The aqueous layer was further extracted with ethyl acetate and the combined organic extracts were dried over Na_2SO_4 and concentrated. Flash chromatography with ethyl acetate/hexane mixtures provided the desired compound as a light yellow semi-solid. MS (FAB): 508 $(M+H)^+$.

Example 2F: (2S)-Methyl-((3S)-((amino-3-phenylmethyl-2-oxo-1-piperidinyl)-3-(4-thiazolyl)propionate.

The resultant compound from Example 2E (2.5 g, 4.9 mmol) was dissolved in glacial acetic acid (10 ml) and then treated with HBr/HOAc (10 ml). After stirring for 45 min, the orange solution was concentrated in vacuo. The residue was dissolved in 50 ml H_2O and washed with CCl_4

(4X). Solid $NaHCO_3$ was added to the aqueous layer to bring the pH to 9 and the aqueous layer was extracted with CH_2Cl_2 (2X) and ethyl acetate (2X). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford a yellow oil (1.8 g). MS(DCI): 374 $(M+H)^+$.

Example 2G: (2S)-Methyl-((3S)-((N-methylpiperazinsulfonyl) amino-3-phenylmethyl-2-oxo-1-piperidinyl)-3-(4-thiazolyl)propionate.

The resultant compound from Example 2F (250 mg, 0.67 mmol) was dissolved in 5 ml dry dimethylformamide. To this solution was added N-methylmorpholine (407 mg, 4 mmol), N,N-dimethylaminopyridine (42 mg, 0.34 mmol) and N-methylpiperidinesulfamoyl chloride (470 mg, 2 mmol). After stirring for 18 hr, the solution was diluted with ethyl acetate (150 ml) and washed with saturated brine (3X), dried (Na_2SO_4) and concentrated in vacuo to afford a yellow oil. Flash chromatography with methanol/chloroform mixtures provided the title compound as a colorless foam (180 mg, 50%). MS(CI): 536 $(M+H)^+$.

Example 2H: (2S)-((3S)-((N-methylpiperazinsulfonyl) amino-3-phenylmethyl-2-oxo-1-piperidinyl)-3-(4-thiazolyl)propionic acid amide of (2S,4S,1'R,2'S)-2-(2'-amino-3'-cyclohexyl-1'-hydroxypropyl)-4-methyltetrahydrofuran.

The resultant compound from Example 2G (500 mg, 0.93 mmol) was dissolved in dioxane (9 ml) and cooled to 0°C under a N_2 atmosphere. A solution of LiOH (98 mg, 2.3 mmol) in water (3 ml) was added dropwise and the solution was stirred for 15 min at 0°C and at 1 hr at

25°C. The reaction was neutralized with HCl/dioxane (500 µl, 2.3 mmol) and the solution was concentrated in vacuo and dried overnight on the HI-vac. The resultant colorless acid, the amine hydrochloride resulting from HCl/dioxane treatment of (4S,5R, 2'S,4'S)-3-(t-butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-dimethyl-5-(4-methyltetrahydrofuran-2-yl)oxazolidine (European Patent Application No. EP0307837, published March 22, 1989) (0.93 mmol), HOBT (377 mg, 2.8 mmol), and N-methylmorpholine (104 mg, 1.02 mmol) were dissolved in dry DMF and cooled to -23°C. To this solution was added EDAC (178 mg, 0.93 mmol) in one portion. The reaction was stirred for 3 h at -23°C, warmed to 25°C, and stirred overnight. The reaction was poured into saturated aqueous $NaHCO_3$ (50 ml) and extracted with ethyl acetate (4X). The combined organic extracts were washed with saturated aqueous NaCl (2X) dried over Na_2SO_4 and concentrated in vacuo to afford a yellow foam. Flash chromatography with methanol/methylene chloride mixtures afforded the product as a colorless powder.Mp 85-89°C. MS(DCI): 746 $(M+H)^+$.

Example 3

(2S)-((3S)-((N-methylpiperazinsulfonyl)-amino-3-phenylmethyl-2-oxo-1-piperidinyl)-3-(4-thiazolyl) propionic acid amide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

The resultant compound from Example 2G (500 mg, 0.93 mmol) was dissolved in dioxane (9 ml) and cooled to 0°C under a N_2 atmosphere. A solution of LiOH (98 mg, 2.3 mmol) in water (3 ml) was added dropwise and the solution was stirred for 15 min at 0°C and at 1 hr at

25°C. The reaction was neutralized with HCl/dioxane (500 µl, 2.3 mmol) and the solution was concentrated in vacuo and dried overnight on the HI-vac. The resultant colorless acid, 2(S)-Amino-1-cyclohexyl-3(R),4(S)-dihydroxy-6-methylheptane (U.S. Patent No. 4,845,079, issued July 4, 1989) (226 mg, 0.93 mmol), HOBT (377 mg, 2.8 mmol), and N-methylmorpholine (104 mg, 1.02 mmol) were dissolved in dry DMF and cooled to -23°C. To this solution was added EDAC (178 mg, 0.93 mmol) in one portion. The reaction was stirred for 3 h at -23°C, warmed to 25°C, and stirred overnight. The reaction was poured into saturated aqueous $NaHCO_3$ (50 ml) and extracted with ethyl acetate (4X). The combined organic extracts were washed with saturated aqueous NaCl (2X) dried over Na_2SO_4 and concentrated in vacuo to afford a yellow oil. Flash chromatography with methanol/methylene chloride mixtures afforded the product as a colorless powder (110 mg, 16%).

Mp 93-97°C. MS(DCI): 747 $(M+H)^+$.

MS(Hi-Res): Calcd. Mass for $C_{37}H_{59}N_6O_6S_2$=747.3937 Measured Mass=747.3929.

Example 4

3-(3-Thiazolyl)-2-(3R-benzyl-4-N-(N-methylpiperazyl)-sulfonyl-2-keto-piperazin-1-yl)-propionic acid Amide of Butyl 5(S)-amino-6-cyclohexyl-4(S)-hydroxy-2(R)-isopropylhexan-amide.

This compound was synthesized following the same procedure as described in Scheme 4B. A minor change was made (see Scheme 10B) at the allylamine stage **68**. The intermediate **68** was sulfonated with N-methylpiperazyl

sulfonyl chloride (J. Med. Chem. **15**, 538, 1972) to give **69** in moderate yield (40-65%). The acid obtained following the hydrolysis of **70** with LiOH was coupled under standard EDAC condition with 5(S)-amino-6-cyclohexyl-4(S)-hydroxy-2(R)-isopropylhexanoic acid-n-butylamide (U.S. Patent No. 4,727,060, issued February 23, 1988) to give the final product **71**. DCI-NH_3-MS, m/e. 816 (MH^+, 60%), 798 (10%), 750 (3%) and 327 (100%); ^1H NMR (300 MHz, $CDCl_3$) δ:8.75 (d,J=2Hz,H), 7.35-7.20 (m,5H), 7.12 (d,J=2Hz,H), 6.58 (d,J=9Hz,H), 6.01 (t,J=5Hz,H), 5.18 (6m,H), 4.26 (dd,J=9.4Hz), 4.06 (m,H), 3.90-3.00 (m), 3.00-2.70 (m), 2.20 (s,3H), 2.20-1.05 (m) and 0.90 (m,9H); Anal. ($C_{44}H_{65}N_7O_6S_2$) C,H,N.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfate, glucoheptonate, glycerophosphate, hemislufate, heptonate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other salts include salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

The compounds of the present invention can also be used in the form of prodrugs which include esters.

Examples of such esters include a hydroxyl-substituted compound of the invention which has been acylated with a blocked or unblocked amino acid residue, a phosphate function, or a hemisuccinate residue. The amino acid esters of particular interest are glycine and lysine; however, other amino acid residues can also be used. Other esters include the compounds of the invention wherein a carboxylic acid group has been esterified to provide esters which include, but are not limited to, methyl, ethyl or benzyl esters. These esters serve as prodrugs of the compounds of the present invention and serve to increase the solubility of these substances in the gastrointestinal tract. The prodrugs are metabolically converted in vivo to parent compound of the invention. The preparation of the pro-drug esters is carried out by reacting a hydroxyl-substituted compound of the invention with an activated amino acyl, phosphoryl or hemisuccinyl derivative. The resulting product is then deprotected to provide the desired pro-drug ester. Prodrugs which are esters of carboxylic acid group containing compounds of the invention are prepared by methods known in the art.

The novel method of this invention is directed to the use of a renin inhibitor for treating, inhibiting, relieving or reversing vascular diseases with respect to functional and/or anatomical abnormalities, especially peripheral vascular diseases and microvascular diseases associated with diabetes mellitus in mammals. These diseases may be, among others, diseases of the retina, diaseases of the skin, diseases of the general circulation, diseases of the kidney, or peripheral, central or autonomic nervous system. All of these diseases may occur as symptoms

associated with the acute or chronic complications of diabetes mellitus. In particular, this invention is directed to the use of a renin inhibitor for treating, inhibiting, relieving or reversing diabetic retinopathy, diabetic nephropathy or diabetic neuropathy.

This invention is also directed to renin inhibitor compositions useful for treating, inhibiting, relieving or reversing microvascular diseases with respect to functional and/or anatomical abnormalities, and especially those diseases associated with diabetes mellitus in mammals. In particular, this invention is directed to renin inhibitor compositions useful for treating, inhibiting, relieving or reversing diabetic retinopathy, diabetic nephropathy or diabetic neuropathy.

While not intending to be bound by any theoretical mechanisms of action, the method and composition of this invention is believed to prevent localized increases in microvascular blood pressure due to locally enhanced activity of the renin-angiotensin-aldosterone system in the microvascular tissues, thus preventing or minimizing leakage from the vascular wall into the extracellular space and thus preventing the damage to the vascular system which would otherwise be caused by such leakage. The method and composition of this invention are both therapeutic and preventative. The method and composition of this invention inhibit or minimize physically or biochemically caused damage to blood vessels, and in particular the development of serious complications of diabetes mellitus where symptoms are not yet detectable; and provide relief by reversing vascular damage already done or inhibiting or minimizing further vascular damage in chronic diabetes mellitus patients where microvascular complications have already developed.

The ability of renin inhibitors to prevent, reverse or inhibit microvascular disease associated with diabetes can be demonstrated by comparing urinary protein excretion in control diabetic Wistar rats with urinary protein excretion in diabetic Wistar rats treated with a renin inhibitor. Wistar rats are made diabetic by streptozocin treatment.

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 10 mg/kg body weight daily and more usually 0.01 to 1 mg/kg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, by inhalation spray, by nasal spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. Topical

administration may also involve the use of ocular inserts. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, dextrose solution, mannitol solution, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating

agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

While the renin inhibitors can be administered as the sole active pharmaceutical agent, they can also be used in combination with insulin and/or a hypoglycemic agent such as an aldose reductase inhibitor or an agent selected from tolbutamide, acetohexamide, tolazamide and chlorpropamide. The renin inhibitors can also be used in combination with vasodilators useful for the treatment of peripheral vascular diseases including, but not limited to, calcium antagonists, beta-blockers and agents such as pentoxifylline and buflomedil. When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

CLAIMS

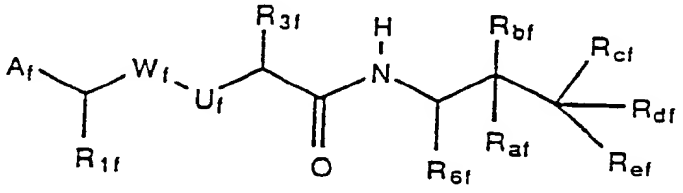
What is claimed is:

1. A method comprising administering to a host in need thereof a therapeutically effective amount of a renin inhibitor for treating, inhibiting, relieving or reversing vascular abnormalities or diseases including peripheral vascular diseases.

2. The method of Claim 1 wherein the vascular disease is a microvascular disease associated with diabetes.

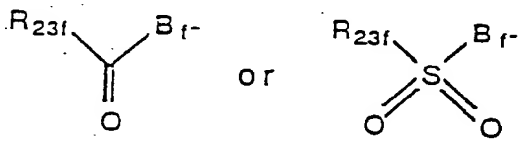
3. The method of Claim 2 wherein the microvascular disease is diabetic retinopathy, daibetic nephropathy or diabetic neuropathy.

4. The method of Claim 1 wherein the renin inhibitor is selected from the group consisting of compounds of the formula:



wherein A_f is hydrogen, loweralkyl, arylalkyl, $-OR_{10f}$ or $-SR_{10f}$ wherein R_{10f} is hydrogen, loweralkyl or aminoalkyl, $-NR_{11f}R_{12f}$ wherein R_{11f}

and R_{12f} are independently selected from hydrogen, loweralkyl, aminoalkyl, cyanoalkyl, hydroxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, (amino)carboxyalkyl, ((N-protected)amino)carboxyalkyl, (alkylamino)carboxyalkyl, ((N-protected)alkylamino)carboxyalkyl, (dialkylamino)carboxyalkyl, (amino)alkoxycarbonylalkyl, ((N-protected)amino)alkoxycarbonylalkyl, (alkyamino)alkoxycarbonylalkyl, ((N-protected)alkylamino)alkoxycarbonylalkyl and (dialkylamino)alkoxycarbonylalkyl;
or A_f is



wherein B_f is NH, alkylamino, S, O, CH_2 or CHOH and R_{13f} is loweralkyl, cycloalkyl, aryl, arylalkyl, alkoxy, alkenyloxy, hydroxyalkoxy, dihydroxyalkoxy, arylalkoxy, arylalkoxyalkyl, amino, alkylamino, dialkylamino, (hydroxyalkyl)(alkyl)amino, (dihydroxyalkyl)(alkyl)amino, aminoalkyl, N-protected-aminoalkyl, alkylaminoalkyl, (N-protected)(alkyl)aminoalkyl, dialkylaminoalkyl, carboxyalkoxyalkyl, (alkoxycarbonyl)alkoxyalkyl, carboxyalkyl, carboxyalkylamino, alkoxycarbonylalkyl, alkoxycarbonyalkylamino, (amino)carboxyalkyl, (amino)carboxyalkylamino, ((N-protected)amino)carboxyalkyl, ((N-protected)amino)-carboxyalkyamino, (alkylamino)carboxyalkyl,

(alkylamino)carboxyalkylamino, ((N-protected)alkylamino)-carboxyalkyl,
((N-protected)alkylamino)carboxyalkylamino,
(dialkylamino)carboxyalkyl,
(dialkylamino)carboxyalkylamino,
(amino)alkoxycarbonylalkyl,
(amino)alkoxycarbonylalkylamino,
((N-protected)amino)alkoxycarbonylalkyl,
((N-protected)amino)- alkoxycarbonylalkylamino,
(alkylamino)alkoxycarbonylalkyl,
(alkylamino)alkoxycarbonylalkylamino,
((N-protected)alkylamino)- alkoxycarbonylalkyl,
((N-protected)alkylamino)alkoxycarbonyl- alkylamino,
(dialkylamino)alkoxycarbonylalkyl,
(dialkylamino)alkoxycarbonylalkylamino, aminocycloalkyl, aminoalkylamino, dialkylaminoalkyl(alkyl)amino, arylalkylamino, arylalkyl(alkyl)amino, alkoxyalkyl(alkyl)amino, (polyalkyoxy)-alkyl(alkyl)amino, di-(alkoxyalkyl)amino, di-(hydroxyalkyl)amino, di-((polyalkoxy)alkyl)amino, polyalkoxy, (polyalkoxy)alkyl, (heterocyclic)alkyl or a substituted or unsubstituted heterocyclic wherein saturated heterocyclics may be unsubstituted, monosubstituted or disubstituted with hydroxy, oxo, amino, alkylamino, dialkylamino, alkoxy, polyalkoxy or loweralkyl; unsaturated heterocyclics may be unsubstituted or monosubstituted with hydroxy, amino, alkylamino, dialkylamino, alkoxy, polyalkoxy or loweralkyl;

W_f is C=O or CHOH;

U_f is CH_2 or NR_2, provided that when W_f is CHOH then U_f is CH_2;

R_{1f} is loweralkyl, cycloalkylmethyl, benzyl, 4-methoxybenzyl, halobenzyl, (1-naphthyl)methyl, (2-naphthyl)methyl, (4-imidazolyl)methyl, (alpha,alpha)-dimethylbenzyl, 1-benzyloxyethyl, phenethyl, phenoxy, thiophenoxy or anilino; provided that when R_{1f} is phenoxy, thiophenoxy or anilino, then B_f is CH_2 or CHOH or A_f is hydrogen;

R_{2f} is hydrogen or loweralkyl;

R_{3f} is loweralkyl, loweralkenyl, ((alkoxy)alkoxy)loweralkyl, (thioalkoxy)alkyl, benzyl or heterocyclic ring substituted methyl;

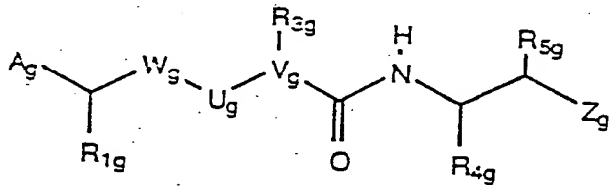
R_{6f} is loweralkyl, cycloalkylmethyl or benzyl;

R_{af} is vinyl, formyl, hydroxymethyl or hydrogen;

R_{df} is hydrogen or loweralkyl;

R_{bf} and R_{ef} are independently selected from OH and NH_2; and

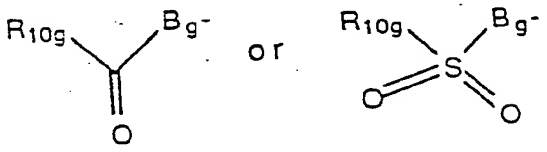
R_{cf} is hydrogen, loweralkyl, vinyl or arylalkyl;



wherein A_g is hydrogen, loweralkyl, aminoalkyl, (alkyl)aminoalkyl, dialkylaminoalkyl, (alkoxy)aminoalkyl, (alkoxy)(alkyl)aminoalkyl, phenylalkyl, (substituted phenyl)alkyl wherein the

phenyl ring is substituted with one, two or three substituents independently selected from loweralkoxy, loweralkyl, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide, naphthylalkyl, (substituted naphthyl)alkyl wherein the naphthyl ring is substituted with one, two or three substituents independently selected from loweralkoxy, loweralkyl, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide, substituted or unsubstituted heterocyclic, where saturated heterocyclics may be unsubstituted, monosubsituted or disubstituted with hydroxy, oxo, amino, alkylamino, dialkylamino, alkoxy, polyalkoxy, loweralkyl, haloalkyl or polyhaloalkyl; unsaturated heterocyclics may be unsubstituted or monosubstituted with hydroxy, amino, alkylamino, dialkylamino, alkoxy, polyalkoxy, loweraklyl, haloalkyl or polyhaloalkyl, or A_g is (unsubstituted heterocyclic)alkyl or (substituted heterocyclic)alkyl wherein unsubstituted or substituted heterocyclic is as defined above, or A_g is $-OR_{7g}$ or $-SR_{7g}$ wherein R_{7g} is hydrogen, loweralkyl, aminoalkyl, (alkyl)aminoalkyl, dialkylaminoalkyl, (alkoxy)aminoalkyl, (alkoxy)(alkyl)aminoalkyl, phenylalkyl, (substituted phenyl)alkyl wherein substituted phenyl is as defined above, naphthylalkyl, (substituted naphthyl)alkyl wherein the substituted naphthyl is as defined above, substituted or unsubstituted heterocyclic as defined above, (unsubstituted heterocyclic)alkyl or (substituted heterocyclic)alkyl wherein unsubstituted or substituted heterocyclic is as defined above, (unsubstituted

heterocyclic)C(O)- or (substituted heterocyclic)C(O)- wherein unsubstituted or substituted heterocyclic is as defined above; or A_g is $-NR_{8g}R_{9g}$ wherein R_{8g} and R_{9g} are independently selected from hydrogen, hydroxy, alkoxy, loweralkyl, aminoalkyl, cyanoalkyl and hydroxyalkyl; or A_g is



wherein B_g is NH, alkylamino, S, O, CH_2, $NHCH_2$ or $CH(OR_{52g})$ wherein R_{52g} is hydrogen, loweralkyl or loweralkylcarbonyl, and R_{10g} is hydrogen, loweralkyl, cycloalkyl, phenyl, substituted phenyl as defined above, naphthyl, substituted naphthyl as defined above, alkoxy, alkenyloxy, hydroxyalkoxy, dihydroxyalkoxy, phenylalkoxy, (substituted phenyl)alkoxy wherein substituted phenyl is as defined above, naphthylalkoxy, (substituted naphthyl)alkoxy wherein substituted naphthyl is as defined above, phenylalkoxyalkyl, (substituted phenyl)alkoxyalkyl wherein substituted phenyl is as defined above, naphthylalkoxyalkyl, (substituted naphthyl)alkoxyalkyl wherein substituted naphthyl is as defined above, thioalkoxyalkyl, loweralkylsulfinylalkyl, loweralkylsulfonylalkyl, phenylthioalkyl, (substituted phenyl)thioalkyl wherein substituted phenyl is as defined above, naphthylthioalkyl, (substituted naphthyl)thioalkyl wherein substituted naphthyl is as defined above, phenylsulfonylalkyl, (substituted phenyl)sulfonylalkyl wherein substituted phenyl is as defined above,

naphthylsulfonylalkyl, (substituted naphthyl)sulfonylalkyl wherein substituted naphthyl is as defined above, amino, alkylamino, dialkylamino, (hydroxyalkyl)(alkyl)amino, (dihydroxyalkyl)(alkyl)amino, aminoalkyl, alkoxycarbonylalkyl, carboxyalkyl, (N-protected)-aminoalkyl, alkylaminoalkyl, (N-protected)(alkyl)aminoalkyl, dialkylaminoalkyl, (heterocyclic)alkyl, a substituted or unsubstituted heterocyclic as defined above, aminocycloalkyl, aminoalkylamino, (dialkylaminoalkyl)(alkyl)amino, phenylalkylamino, (substituted phenyl)alkylamino wherein substituted phenyl is as defined above, naphthylalkylamino, (substituted naphthyl)alkylamino wherein substituted naphthyl is as defined above, (phenylalkyl)(alkyl)amino, ((substituted phenyl)alkyl)(alkyl)amino wherein substituted phenyl is as defined above, (naphthylalkyl)(alkyl)amino, ((substituted naphthyl)alkyl)(alkyl)amino wherein substituted naphthyl is as defined above, alkoxyalkyl(alkyl)amino, (polyalkoxy)alkyl(alkyl)amino, di-(alkoxyalkyl)amino, di-(hydroxyalkyl)amino, di-((polyalkoxy)alkyl)amino, ((heterocyclic)alkyl)(alkyl)amino, ((heterocyclic)alkyl)amino, (heterocyclic)(alkyl)amino, (alkylaminoalkyl)(alkyl)amino, (dialkylaminoalkyl)(alkyl)amino, ((alkoxy)(alkyl)aminoalkyl)(alkyl)amino, ((alkoxy)aminoalkyl)(alkyl)amino, polyalkoxy or (polyalkoxy)alkyl; or A_g is $R_{41g}CH(OH)CH_2-$ or $R_{41g}CH(OH)CH(OH)-$ wherein R_{41g} is loweralkyl, cycloalkyl, phenyl, substituted phenyl as defined above, naphthyl, substituted naphthyl as defined above,

phenylalkyl, (substituted phenyl)alkyl wherein substituted phenyl is as defined above, naphthylalkyl, (substituted naphthyl)alkyl wherein substituted naphthyl is as defined above, phenylalkoxyalkyl, (substituted phenyl)alkoxyalkyl wherein substituted phenyl is as defined above, naphthylalkoxyalkyl, (substituted naphthyl)alkoxyalkyl wherein substituted naphthyl is as defined above, thioalkoxyalkyl, loweralkylsulfinylalkyl, loweralkylsulfonylalkyl, phenylthioalkyl, (substituted phenyl)thioalkyl wherein substituted phenyl is as defined above, naphthylthioalkyl, (substituted naphthyl)thioalkyl wherein substituted naphthyl is as defined above, phenylsulfonylalkyl, (substituted phenyl)sulfonylalkyl wherein substituted phenyl is as defined above, naphthylsulfonylalkyl, (substituted naphthyl)sulfonylalkyl wherein substituted naphthyl is as defined above, aminoalkyl, alkoxycarbonylalkyl, carboxyalkyl, (N-protected)aminoalkyl, alkylaminoalkyl, (N-protected)(alkyl)aminoalkyl, dialkylaminoalkyl, heterocyclicalkyl, a substituted or unsubstituted heterocyclic as defined above, aminocycloalkyl or (polyalkoxy)alkyl;

W_g is C=O, CHOH or NR_{2g} wherein R_{2g} is hydrogen or loweralkyl;

U_g is C=O, CH_2 or NR_{2g} wherein R_{2g} is hydrogen or loweralkyl, with the proviso that when W_g is CHOH then U_g is CH_2 and with the proviso that U_g is C=O or CH_2 when W_g is NR_{2g};

V_g is CH, C(OH) or C(halogen) with the proviso that V_g is CH when U_g is NR_{2g};

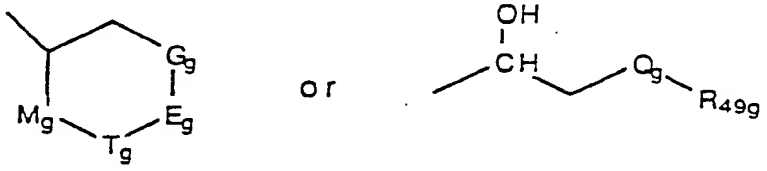
R_{1g} is loweralkyl, cycloalkylalkyl, benzyl, (alpha, alpha)-dimethylbenzyl, 4-methoxybenzyl, halobenzyl, 4-hydroxybenzyl, (1-naphthyl)methyl, (2-naphthyl)methyl, (unsubstituted heterocyclic)methyl, (substituted heterocyclic)methyl wherein unsubstituted or substituted heterocyclic is as defined above, phenethyl, 1-benzyloxyethyl, phenoxy, thiophenoxy or anilino, provided that B_g is CH_2 or CHOH or A_g is hydrogen when R_{1g} is phenoxy, thiophenoxy or anilino;

R_{3g} is loweralkyl, loweralkenyl, ((alkoxy)alkoxy)alkyl, carboxyalkyl, (thioalkoxy)alkyl, azidoalkyl, aminoalkyl, (alkyl)aminoalkyl, dialkylaminoalkyl, (alkoxy)(alkyl)aminoalkyl, (alkoxy)aminoalkyl, benzyl or heterocyclic ring substituted methyl;

R_{4g} is loweralkyl, cycloalkylmethyl or benzyl;

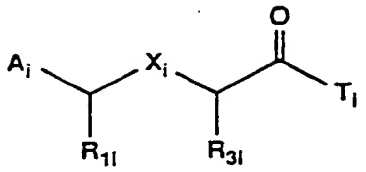
R_{5g} is OH or NH_2; and

Z_g is



wherein M_g is O, S or NH, T_g is C=O, C=S, S, S(O), $S(O)_2$ or CH_2, E_g is O, S, NR_{6g} wherein R_{6g} is hydrogen, loweralkyl, hydroxyalkyl, hydroxy, alkoxy, amino, or alkylamino, or E_g is $CR_{6g}R_{42g}$ wherein

R_{6g} is as defined above and R_{42g} is hydrogen or loweralkyl or E_g is $C=CR_{43g}R_{44g}$ wherein R_{43g} and R_{44g} are independently selected from hydrogen and loweralkyl, G_g is absent, CH_2, or NR_{11g} wherein R_{11g} is hydrogen or loweralkyl, with the proviso that when G_g is NR_{11g} then R_{6g} is loweralkyl or hydroxyalkyl, Q_g is $CR_{45g}R_{46g}$ wherein R_{45g} and R_{46g} are independently selected from hydrogen and loweralkyl or Q_g is $C=CR_{47g}R_{48g}$ wherein R_{47g} and R_{48g} are independently selected from hydrogen and loweralkyl, and R_{49g} is $-CH_2OH$, carboxy, alkoxycarbonyl or $-CONR_{50g}R_{51g}$ wherein R_{50g} is hydrogen or loweralkyl and R_{51g} is hydrogen, loweralkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl or alkoxyalkyl;



wherein A_i is

(I) $R_{5i}C(O)-(CH_2)_{w"}-$ wherein

1) w" is 0 to 4 and

2) R_{5i} is

i) hydroxy,

ii) alkoxy,

iii) thioalkoxy,

iv) amino or

v) substituted amino;

(II) alkylsulfonyl, (aryl)sulfonyl or (heterocyclic)sulfonyl;

(III) aryl, arylalkyl, heterocyclic or (heterocyclic)alkyl; or

(IV) $R_{90i}-$ or $R_{90i}NHC(O)-$ wherein R_{90i} is a C_1 to C_4 straight or branched carbon chain substituted by a substituent selected from

1) carboxy,

2) alkoxycarbonyl,

3) alkylsulfonyl,

4) aryl,

5) arylsulfonyl,

6) heterocyclic or

7) (heterocyclic)sulfonyl);

R_{1i} is

(I) hydrogen,

(II) loweralkyl,

(III) loweralkenyl,
(IV) cycloalkylalkyl,
(V) cycloalkenylalkyl,
(VI) aryloxyalkyl,
(VII) thioaryloxyalkyl,
(VIIII) arylalkoxyalkyl,
(IX) arylthioalkoxyalkyl or
(X) a C_1 to C_3 straight or branched carbon chain substituted by a substituent selected from
1) alkoxy,
2) thioalkoxy,
3) aryl and
6) heterocyclic;

X_i is
(I) CH_2,
(II) CHOH,
(III) C(O),
(IV) NH,
(V) O,
(VI) S,
(VII) S(O),
(VIII) SO_2,
(IX) N(O) or
(X) -P(O)O-;

R_{3i} is
(I) loweralkyl,
(II) haloalkyl,
(III) loweralkenyl,
(IV) cycloalkylalkyl,
(V) cycloalkenylalkyl,

(VI) alkoxyalkyl,

(VII) thioalkoxyalkyl,

(VIII) (alkoxyalkoxy)alkyl,

(IX) hydroxyalkyl,

(X) $-(CH_2)_{ee}NHR_{12i}$

wherein

1) ee is 1 to 3 and

2) R_{12i} is

i) hydrogen,

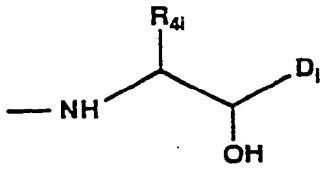
ii) loweralkyl or

iii) an N-protecting group;

(XI) arylalkyl or

(XII) (heterocyclic)alkyl; and

T_i is



wherein R_{4i} is

(I) loweralkyl,

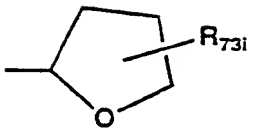
(II) cycloalkylalkyl

(III) cycloalkenylalkyl or

(III) arylalkyl; and

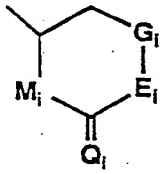
D_i is

(I)



wherein R_{73i} is loweralkyl,

(II)



wherein

1) M_i is
   i) O,
   ii) S or
   iii) NH;
2) Q_i is
   i) O or
   ii) S;
3) Ei is
   i) O,
   ii) S,
   iii) CHR_{73i} wherein R_{73i} is loweralkyl,
   iv) $C=CH_2$ or
   v) NR_{18i} wherein R_{18i} is
      a) hydrogen,
      b) loweralkyl,
      c) hydroxyalkyl,
      d) hydroxy,
      e) alkoxy,

f) amino or

g) alkylamino;

and

4) G_i is

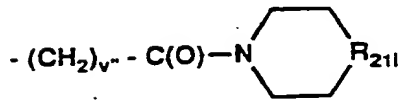
i) absent,

ii) CH_2 or

iii) NR_{19i} wherein R_{19i} is hydrogen or loweralkyl,

with the proviso that when G_i is NR_{19i}, then R_{18i} is loweralkyl or hydroxyalkyl;

(III)



wherein

1) v" is 0 or 1 and

2) R_{21i} is

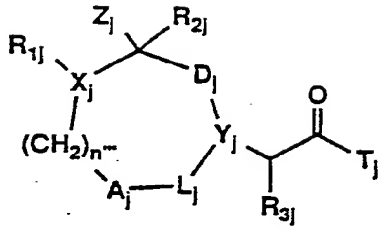
i) NH,

ii) O,

iii) S or

iv) SO_2; or

(IV) a substituted methylene group; and



wherein X_j is

(I) N,

(II) O or

(III) CH;

R_{1j} is

(I) absent,

(II) hydrogen,

(III) an N-protecting group,

(IV) aryl,

(V) heterocyclic, or

(VI) R_{6j}-Q_j- wherein

1) R_{6j} is

i) loweralkyl,

ii) amino,

iii) alkylamino,

iv) dialkylamino,

v) (alkoxyalkyl)(alkyl)amino,

vi) (alkoxyalkoxyalkyl)(alkyl)amino,

vii) aryl,

viii) arylalkyl,

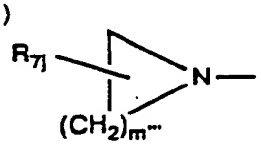
ix) aminoalkyl,

x) (N-protected)aminoalkyl,

xi) alkoxy,

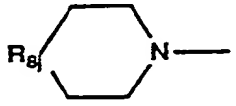
xii) substituted loweralkyl wherein the substituent is selected from alkoxy, thioalkoxy, halogen, alkylamino, (N-protected)(alkyl)amino and dialkylamino,

xiii)



wherein m''' is 1 to 5 and R_{7j} is hydrogen, hydroxy, alkoxy, thioalkoxy, alkoxyalkoxy, polyalkoxy, amino, (N-protected)amino, alkylamino, (N-protected)(alkyl)amino or dialkylamino; or

xiv)



wherein R_{8j} is O, S, SO_2, O=C or $R_{9j}N$ wherein R_{9j} is hydrogen, loweralkyl or an N-protecting group; and

2) Q_j is

i) C=O or

ii) CH_2,

with the proviso that X_j is N when R_{1j} is an N-protecting group;

(VII) $R_{54j}S(O)_2$- wherein R_{54j} is

1) amino,

2) alkylamino,

3) dialkylamino,

4) loweralkyl,
5) haloalkyl,
6) aryl,
7) p-biphenyl,
8) heterocyclic or

(VIII) $(R_{55j})_2P(O)-$ wherein R_{55j} is
1) alkoxy,
2) alkylamino or
3) dialkylamino;

A_j and L_j are independently selected from
(I) absent,
(II) C=O,
(III) SO_2 and
(IV) CH_2;

D_j is
(I) C=O,
(II) SO_2 or
(III) CH_2;

Y_j is
(I) N or
(II) CH;

R_{2j} is
(I) hydrogen,
(II) loweralkyl,
(III) cycloalkylalkyl,
(IV) $-CH_2-R_{10j}-(CH_2)_{q'''}-R_{11j}$ wherein
1) q''' is 0, 1 or 2,

2) R_{10j} is absent or R_{10j} is O, NH or S only when q''' is 1 or 2, and

3) R_{11j} is

i) aryl or

ii) heterocyclic;

Z_j is

(I) hydrogen or

(II) $-R_{28j}C(O)R_{29j}$, $-R_{28j}S(O)_2R_{29j}$ or $-R_{28j}C(S)R_{29j}$ wherein

1) R_{28j} is

i) NH,

ii) $-N(R_{200j})-$ wherein R_{200j} is loweralkyl or benzyl or

iii) CH_2 and

2) R_{29j} is

i) alkoxy,

ii) benzyloxy,

iii) alkylamino,

iv) dialkylamino,

v) aryl or

vi) heterocyclic;

R_{3j} is

(I) hydrogen,

(II) loweralkyl,

(III) loweralkenyl,

(IV) cycloalkylalkyl,

(V) cycloalkenylalkyl,

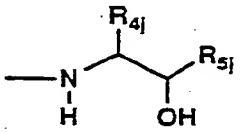
(VI) alkoxyalkyl,

(VII) thioalkoxyalkyl,

(VIIII) (alkoxyalkoxy)alkyl,
(IX) (polyalkoxy)alkyl,
(X) arylalkyl or
(XI) (heterocyclic)alkyl;

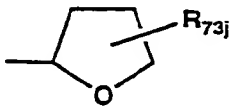
n''' is 0 or 1; and

T_j



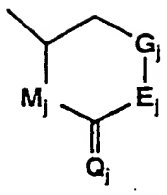
wherein R_{4j} is
(I) loweralkyl,
(II) cycloalkylalkyl or
(III) arylalkyl; and

R_{5j} is
(I)



wherein R_{73j} is loweralkyl,

(II)



wherein

1) M_j is
   i) O,
   ii) S or
   iii) NH;
2) Q_j is
   i) O or
   ii) S;
3) E_j is
   i) O,
   ii) S,
   iii) CHR_{61j} wherein R_{61j} is loweralkyl,
   iv) $C=CH_2$ or
   v) NR_{18j} wherein R_{18j} is
      a) hydrogen,
      b) loweralkyl,
      c) hydroxyalkyl,
      d) hydroxy,
      e) alkoxy,
      f) amino or
      g) alkylamino;

and

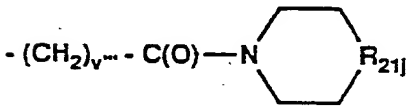
4) G_j is
   i) absent,

ii) CH_2 or

iii) NR_{19j} wherein R_{19j} is hydrogen or loweralkyl,

with the proviso that when G_j is NR_{19j}, then R_{18j} is loweralkyl or hydroxyalkyl;

(III)



wherein

1) v''' is 0 or 1 and

2) R_{21j} is

i) NH,

ii) O,

iii) S or

iv) SO_2; or

(IV) a substituted methylene group;

or a pharmaceutically acceptable salt, ester or prodrug thereof.

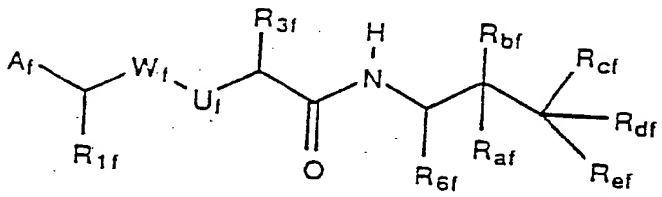
5. The method of Claim 4 wherein the renin inhibitor is selected from the group consisting of:
H-((beta,beta-dimethyl)-beta-Ala)-(4-OCH_3)Phe-His amide of 2(S)-amino-1-cyclohexyl-3(R),4(S)-dihydroxy-6-methylheptane;
2(S)-(1(S)-(4-(Methoxymethoxy)piperidin-1-yl)carbonyl-2-phenyl)ethoxyhexanoic acid amide of 3-(4-morpholinyl)propyl-5-(S)-amino-6-cyclohexyl-4(S)-hydroxy-2(S)isopropylhexanamide;
2(S)-((3(S)-((N-methylpiperazinsulfonyl)amino-3-phenyl-methyl-2-oxo-1-piperidinyl)-3-(4-thiazolyl)propionic acid amide of (2S,4S,1'R,2'S)-2-(2'-amino-3'-cylcohexyl-1'-hydroxy-propyl)-4-methyltetrahydrofuran;
2(S)-((3(S)-((N-methylpiperazinsulfonyl)amino-3-phenyl-methyl-2-oxo-1-piperidinyl)-3-(4-thiazolyl)propionic acid amide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;
3-(3-Thiazolyl)-2-(3R-benzyl-4-N-(N-methylpiperazinyl)-sulfonyl-2-keto-piperazin-1-yl)propionic aicd amide of Butyl 5(S)-amino-6-cyclohexyl-4(S)-hydroxy-2(R)-isopropylhexanamide; and
2(R)-2-Benzyl-3-((2-methoxyethoxymethoxyethyl)methylamino-carbonyl)propionyl-His amide of (2'S,1'R,5S)3-Ethyl-5-(1'-hdyroxy-2'-amino-3'cyclohexyl-propyl)oxazolidin-2-one;
or a pharmaceutically acceptable salt, ester or prodrug thereof.

6. A pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically effective amount of a renin inhibitor for treating, inhibiting, relieving or reversing vascular abnormalities or diseases including peripheral vascular diseases.

7. The composition of Claim 10 wherein the vascular disease is a microvascular disease associated with diabetes.

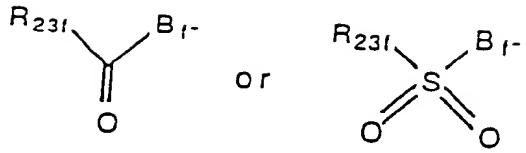
8. The composition of Claim 11 wherein the microvascular disease is diabetic retinopathy, diabetic nephropathy or diabetic neuropathy.

9. The composition of Claim 6 wherein the renin inhibitor is selected from the group consisting of compounds of the formula:



wherein A_f is hydrogen, loweralkyl, arylalkyl, $-OR_{10f}$ or $-SR_{10f}$ wherein R_{10f} is hydrogen, loweralkyl or aminoalkyl, $-NR_{11f}R_{12f}$ wherein R_{11f} and R_{12f} are independently selected from hydrogen, loweralkyl, aminoalkyl, cyanoalkyl, hydroxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, (amino)carboxyalkyl, ((N-protected)amino)carboxyalkyl, (alkylamino)carboxyalkyl, ((N-protected)alkylamino)carboxyalkyl, (dialkylamino)carboxyalkyl, (amino)alkoxycarbonylalkyl, ((N-protected)amino)alkoxycarbonylalkyl, (alkyamino)alkoxycarbonylalkyl, ((N-protected)alkylamino)alkoxycarbonylalkyl and (dialkylamino)alkoxycarbonylalkyl;

or A_f is



wherein B_f is NH, alkylamino, S, O, CH_2 or CHOH and R_{13f} is loweralkyl, cycloalkyl, aryl, arylalkyl, alkoxy, alkenyloxy, hydroxyalkoxy, dihydroxyalkoxy, arylalkoxy, arylalkoxyalkyl, amino, alkylamino, dialkylamino, (hydroxyalkyl)(alkyl)amino, (dihydroxyalkyl)(alkyl)amino, aminoalkyl, N-protected-aminoalkyl, alkylaminoalkyl, (N-protected)(alkyl)aminoalkyl, dialkylaminoalkyl, carboxyalkoxyalkyl, (alkoxycarbonyl)alkoxyalkyl, carboxyalkyl, carboxyalkylamino, alkoxycarbonylalkyl, alkoxycarbonyalkylamino, (amino)carboxyalkyl, (amino)carboxyalkylamino, ((N-protected)amino)carboxyalkyl, ((N-protected)amino)-carboxyalkyamino, (alkylamino)carboxyalkyl, (alkylamino)carboxyalkylamino, ((N-protected)alkylamino)-carboxyalkyl, ((N-protected)alkylamino)carboxyalkylamino, (dialkylamino)carboxyalkyl, (dialkylamino)carboxyalkylamino, (amino)alkoxycarbonylalkyl, (amino)alkoxycarbonylalkylamino, ((N-protected)amino)alkoxycarbonylalkyl, ((N-protected)amino)- alkoxycarbonylalkylamino, (alkylamino)alkoxycarbonylalkyl, (alkylamino)alkoxycarbonylalkylamino, ((N-protected)alkylamino)- alkoxycarbonylalkyl, ((N-protected)alkylamino)alkoxycarbonyl- alkylamino,

(dialkylamino)alkoxycarbonylalkyl, (dialkylamino)alkoxycarbonylalkylamino, aminocycloalkyl, aminoalkylamino, dialkylaminoalkyl(alkyl)amino, arylalkylamino, arylalkyl(alkyl)amino, alkoxyalkyl(alkyl)amino, (polyalkyoxy)-alkyl(alkyl)amino, di-(alkoxyalkyl)amino, di-(hydroxyalkyl)amino, di-((polyalkoxy)alkyl)amino, polyalkoxy, (polyalkoxy)alkyl, (heterocyclic)alkyl or a substituted or unsubstituted heterocyclic wherein saturated heterocyclics may be unsubstituted, monosubstituted or disubstituted with hydroxy, oxo, amino, alkylamino, dialkylamino, alkoxy, polyalkoxy or loweralkyl; unsaturated heterocyclics may be unsubstituted or monosubstituted with hydroxy, amino, alkylamino, dialkylamino, alkoxy, polyalkoxy or loweralkyl;

W_f is C=O or CHOH;

U_f is CH_2 or NR_2, provided that when W_f is CHOH then U_f is CH_2;

R_{1f} is loweralkyl, cycloalkylmethyl, benzyl, 4-methoxybenzyl, halobenzyl, (1-naphthyl)methyl, (2-naphthyl)methyl, (4-imidazolyl)methyl, (alpha,alpha)-dimethylbenzyl, 1-benzyloxyethyl, phenethyl, phenoxy, thiophenoxy or anilino; provided that when R_{1f} is phenoxy, thiophenoxy or anilino, then B_f is CH_2 or CHOH or A_f is hydrogen;

R_{2f} is hydrogen or loweralkyl;

R_{3f} is loweralkyl, loweralkenyl, ((alkoxy)alkoxy)loweralkyl, (thioalkoxy)alkyl, benzyl or heterocyclic ring substituted methyl;

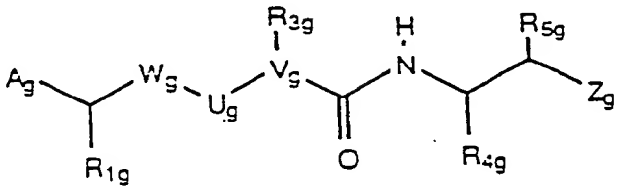
R_{6f} is loweralkyl, cycloalkylmethyl or benzyl;

R_{af} is vinyl, formyl, hydroxymethyl or hydrogen;

R_{df} is hydrogen or loweralkyl;

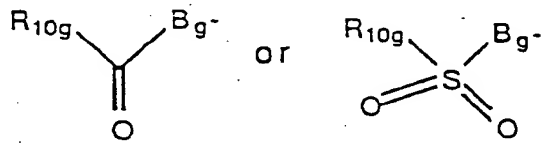
R_{bf} and R_{ef} are independently selected from OH and NH_2; and

R_{cf} is hydrogen, loweralkyl, vinyl or arylalkyl;



wherein A_g is hydrogen, loweralkyl, aminoalkyl, (alkyl)aminoalkyl, dialkylaminoalkyl, (alkoxy)aminoalkyl, (alkoxy)(alkyl)aminoalkyl, phenylalkyl, (substituted phenyl)alkyl wherein the phenyl ring is substituted with one, two or three substituents independently selected from loweralkoxy, loweralkyl, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide, naphthylalkyl, (substituted naphthyl)alkyl wherein the naphthyl ring is substituted with one, two or three substituents independently selected from loweralkoxy, loweralkyl, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide, substituted or unsubstituted heterocyclic, where saturated heterocyclics may be unsubstituted, monosubsituted or disubstituted with hydroxy, oxo, amino, alkylamino, dialkylamino, alkoxy, polyalkoxy, loweralkyl, haloalkyl

or polyhaloalkyl; unsaturated heterocyclics may be unsubstituted or monosubstituted with hydroxy, amino, alkylamino, dialkylamino, alkoxy, polyalkoxy, loweraklyl, haloalkyl or polyhaloalkyl, or A_g is (unsubstituted heterocyclic)alkyl or (substituted heterocyclic)alkyl wherein unsubstituted or substituted heterocyclic is as defined above, or A_g is $-OR_{7g}$ or $-SR_{7g}$ wherein R_{7g} is hydrogen, loweralkyl, aminoalkyl, (alkyl)aminoalkyl, dialkylaminoalkyl, (alkoxy)aminoalkyl, (alkoxy)(alkyl)aminoalkyl, phenylalkyl, (substituted phenyl)alkyl wherein substituted phenyl is as defined above, naphthylalkyl, (substituted naphthyl)alkyl wherein the substituted naphthyl is as defined above, substituted or unsubstituted heterocyclic as defined above, (unsubstituted heterocyclic)alkyl or (substituted heterocyclic)alkyl wherein unsubstituted or substituted heterocyclic is as defined above, (unsubstituted heterocyclic)C(O)- or (substituted heterocyclic)C(O)- wherein unsubstituted or substituted heterocyclic is as defined above; or A_g is $-NR_{8g}R_{9g}$ wherein R_{8g} and R_{9g} are independently selected from hydrogen, hydroxy, alkoxy, loweralkyl, aminoalkyl, cyanoalkyl and hydroxyalkyl; or A_g is



wherein B_g is NH, alkylamino, S, O, CH_2, $NHCH_2$ or $CH(OR_{52g})$ wherein R_{52g} is hydrogen, loweralkyl or loweralkylcarbonyl, and R_{10g} is hydrogen, loweralkyl,

cycloalkyl, phenyl, substituted phenyl as defined above, naphthyl, substituted naphthyl as defined above, alkoxy, alkenyloxy, hydroxyalkoxy, dihydroxyalkoxy, phenylalkoxy, (substituted phenyl)alkoxy wherein substituted phenyl is as defined above, naphthylalkoxy, (substituted naphthyl)alkoxy wherein substituted naphthyl is as defined above, phenylalkoxyalkyl, (substituted phenyl)alkoxyalkyl wherein substituted phenyl is as defined above, naphthylalkoxyalkyl, (substituted naphthyl)alkoxyalkyl wherein substituted naphthyl is as defined above, thioalkoxyalkyl, loweralkylsulfinylalkyl, loweralkylsulfonylalkyl, phenylthioalkyl, (substituted phenyl)thioalkyl wherein substituted phenyl is as defined above, naphthylthioalkyl, (substituted naphthyl)thioalkyl wherein substituted naphthyl is as defined above, phenylsulfonylalkyl, (substituted phenyl)sulfonylalkyl wherein substituted phenyl is as defined above, naphthylsulfonylalkyl, (substituted naphthyl)sulfonylalkyl wherein substituted naphthyl is as defined above, amino, alkylamino, dialkylamino, (hydroxyalkyl)(alkyl)amino, (dihydroxyalkyl)(alkyl)amino, aminoalkyl, alkoxycarbonylalkyl, carboxyalkyl, (N-protected)-aminoalkyl, alkylaminoalkyl, (N-protected)(alkyl)aminoalkyl, dialkylaminoalkyl, (heterocyclic)alkyl, a substituted or unsubstituted heterocyclic as defined above, aminocycloalkyl, aminoalkylamino, (dialkylaminoalkyl)(alkyl)amino, phenylalkylamino, (substituted phenyl)alkylamino wherein substituted phenyl is as defined above, naphthylalkylamino, (substituted naphthyl)alkylamino wherein substituted naphthyl is as defined above,

(phenylalkyl)(alkyl)amino, ((substituted phenyl)alkyl)(alkyl)amino wherein substituted phenyl is as defined above, (naphthylalkyl)(alkyl)amino, ((substituted naphthyl)alkyl)(alkyl)amino wherein substituted naphthyl is as defined above, alkoxyalkyl(alkyl)amino, (polyalkoxy)alkyl(alkyl)amino, di-(alkoxyalkyl)amino, di-(hydroxyalkyl)amino, di-((polyalkoxy)alkyl)amino, ((heterocyclic)alkyl)(alkyl)amino, ((heterocyclic)alkyl)amino, (heterocyclic)(alkyl)amino, (alkylaminoalkyl)(alkyl)amino, (dialkylaminoalkyl)(alkyl)amino, ((alkoxy)(alkyl)aminoalkyl)(alkyl)amino, ((alkoxy)aminoalkyl)(alkyl)amino, polyalkoxy or (polyalkoxy)alkyl; or A_g is $R_{41g}CH(OH)CH_2-$ or $R_{41g}CH(OH)CH(OH)-$ wherein R_{41g} is loweralkyl, cycloalkyl, phenyl, substituted phenyl as defined above, naphthyl, substituted naphthyl as defined above, phenylalkyl, (substituted phenyl)alkyl wherein substituted phenyl is as defined above, naphthylalkyl, (substituted naphthyl)alkyl wherein substituted naphthyl is as defined above, phenylalkoxyalkyl, (substituted phenyl)alkoxyalkyl wherein substituted phenyl is as defined above, naphthylalkoxyalkyl, (substituted naphthyl)alkoxyalkyl wherein substituted naphthyl is as defined above, thioalkoxyalkyl, loweralkylsulfinylalkyl, loweralkylsulfonylalkyl, phenylthioalkyl, (substituted phenyl)thioalkyl wherein substituted phenyl is as defined above, naphthylthioalkyl, (substituted naphthyl)thioalkyl wherein substituted naphthyl is as defined above, phenylsulfonylalkyl, (substituted phenyl)sulfonylalkyl wherein substituted phenyl is as defined above, naphthylsulfonylalkyl, (substituted

naphthyl)sulfonylalkyl wherein substituted naphthyl is as defined above, aminoalkyl, alkoxycarbonylalkyl, carboxyalkyl, (N-protected)aminoalkyl, alkylaminoalkyl, (N-protected)(alkyl)aminoalkyl, dialkylaminoalkyl, heterocyclicalkyl, a substituted or unsubstituted heterocyclic as defined above, aminocycloalkyl or (polyalkoxy)alkyl;

W_g is C=O, CHOH or NR_{2g} wherein R_{2g} is hydrogen or loweralkyl;

U_g is C=O, CH_2 or NR_{2g} wherein R_{2g} is hydrogen or loweralkyl, with the proviso that when W_g is CHOH then U_g is CH_2 and with the proviso that U_g is C=O or CH_2 when W_g is NR_{2g};

V_g is CH, C(OH) or C(halogen) with the proviso that V_g is CH when U_g is NR_{2g};

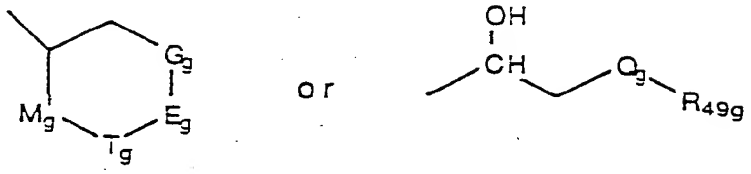
R_{1g} is loweralkyl, cycloalkylalkyl, benzyl, (alpha, alpha)-dimethylbenzyl, 4-methoxybenzyl, halobenzyl, 4-hydroxybenzyl, (1-naphthyl)methyl, (2-naphthyl)methyl, (unsubstituted heterocyclic)methyl, (substituted heterocyclic)methyl wherein unsubstituted or substituted heterocyclic is as defined above, phenethyl, 1-benzyloxyethyl, phenoxy, thiophenoxy or anilino, provided that B_g is CH_2 or CHOH or A_g is hydrogen when R_{1g} is phenoxy, thiophenoxy or anilino;

R_{3g} is loweralkyl, loweralkenyl, ((alkoxy)alkoxy)alkyl, carboxyalkyl, (thioalkoxy)alkyl, azidoalkyl, aminoalkyl, (alkyl)aminoalkyl, dialkylaminoalkyl, (alkoxy)(alkyl)aminoalkyl, (alkoxy)aminoalkyl, benzyl or heterocyclic ring substituted methyl;

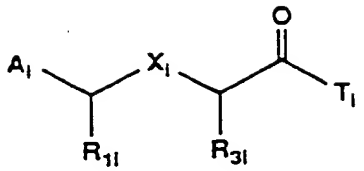
R_{4g} is loweralkyl, cycloalkylmethyl or benzyl;

R_{5g} is OH or NH_2; and

Z_g is



wherein M_g is O, S or NH, T_g is C=O, C=S, S, S(O), $S(O)_2$ or CH_2, E_g is O, S, NR_{6g} wherein R_{6g} is hydrogen, loweralkyl, hydroxyalkyl, hydroxy, alkoxy, amino, or alkylamino, or E_g is $CR_{6g}R_{42g}$ wherein R_{6g} is as defined above and R_{42g} is hydrogen or loweralkyl or E_g is $C=CR_{43g}R_{44g}$ wherein R_{43g} and R_{44g} are independently selected from hydrogen and loweralkyl, G_g is absent, CH_2, or NR_{11g} wherein R_{11g} is hydrogen or loweralkyl, with the proviso that when G_g is NR_{11g} then R_{6g} is loweralkyl or hydroxyalkyl, Q_g is $CR_{45g}R_{46g}$ wherein R_{45g} and R_{46g} are independently selected from hydrogen and loweralkyl or Q_g is $C=CR_{47g}R_{48g}$ wherein R_{47g} and R_{48g} are independently selected from hydrogen and loweralkyl, and R_{49g} is $-CH_2OH$, carboxy, alkoxycarbonyl or $-CONR_{50g}R_{51g}$ wherein R_{50g} is hydrogen or loweralkyl and R_{51g} is hydrogen, loweralkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl or alkoxyalkyl;



wherein A_i is

(I) $R_{5i}C(O)-(CH_2)_{w"}-$ wherein

1) w" is 0 to 4 and

2) R_{5i} is

i) hydroxy,

ii) alkoxy,

iii) thioalkoxy,

iv) amino or

v) substituted amino;

(II) alkylsulfonyl, (aryl)sulfonyl or (heterocyclic)sulfonyl;

(III) aryl, arylalkyl, heterocyclic or (heterocyclic)alkyl; or

(IV) $R_{90i}-$ or $R_{90i}NHC(O)-$ wherein R_{90i} is a C_1 to C_4 straight or branched carbon chain substituted by a substituent selected from

1) carboxy,

2) alkoxycarbonyl,

3) alkylsulfonyl,

4) aryl,

5) arylsulfonyl,

6) heterocyclic or

7) (heterocyclic)sulfonyl);

R_{1i} is

(I) hydrogen,

(II) loweralkyl,

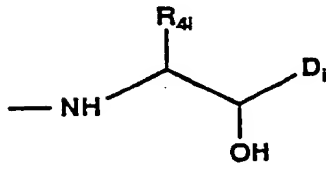
(III) loweralkenyl,
(IV) cycloalkylalkyl,
(V) cycloalkenylalkyl,
(VI) aryloxyalkyl,
(VII) thioaryloxyalkyl,
(VIIII) arylalkoxyalkyl,
(IX) arylthioalkoxyalkyl or
(X) a C_1 to C_3 straight or branched carbon chain substituted by a substituent selected from
1) alkoxy,
2) thioalkoxy,
3) aryl and
6) heterocyclic;

X_i is
(I) CH_2,
(II) CHOH,
(III) C(O),
(IV) NH,
(V) O,
(VI) S,
(VII) S(O),
(VIII) SO_2,
(IX) N(O) or
(X) -P(O)O-;

R_{3i} is
(I) loweralkyl,
(II) haloalkyl,
(III) loweralkenyl,
(IV) cycloalkylalkyl,
(V) cycloalkenylalkyl,

(VI) alkoxyalkyl,
(VII) thioalkoxyalkyl,
(VIII) (alkoxyalkoxy)alkyl,
(IX) hydroxyalkyl,
(X) $-(CH_2)_{ee}NHR_{12i}$
wherein
1) ee is 1 to 3 and
2) R_{12i} is
i) hydrogen,
ii) loweralkyl or
iii) an N-protecting group;
(XI) arylalkyl or
(XII) (heterocyclic)alkyl; and

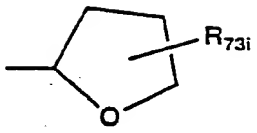
T_i is



wherein R_{4i} is
(I) loweralkyl,
(II) cycloalkylalkyl
(III) cycloalkenylalkyl or
(III) arylalkyl; and

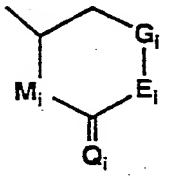
D_i is

(I)



wherein R_{73i} is loweralkyl,

(II)



wherein

1) M_i is
   i) O,
   ii) S or
   iii) NH;
2) Q_i is
   i) O or
   ii) S;
3) Ei is
   i) O,
   ii) S,
   iii) CHR_{73i} wherein R_{73i} is loweralkyl,
   iv) $C=CH_2$ or
   v) NR_{18i} wherein R_{18i} is
      a) hydrogen,
      b) loweralkyl,
      c) hydroxyalkyl,
      d) hydroxy,
      e) alkoxy,

f) amino or

g) alkylamino;

and

4) G_i is

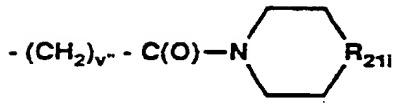
i) absent,

ii) CH_2 or

iii) NR_{19i} wherein R_{19i} is hydrogen or loweralkyl,

with the proviso that when G_i is NR_{19i}, then R_{18i} is loweralkyl or hydroxyalkyl;

(III)



wherein

1) v" is 0 or 1 and

2) R_{21i} is

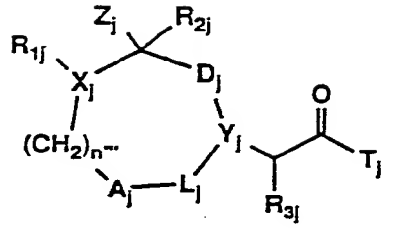
i) NH,

ii) O,

iii) S or

iv) SO_2; or

(IV) a substituted methylene group; and



wherein X_j is

(I) N,

(II) O or

(III) CH;

R_{1j} is

(I) absent,

(II) hydrogen,

(III) an N-protecting group,

(IV) aryl,

(V) heterocyclic, or

(VI) R_{6j}-Q_j- wherein

1) R_{6j} is

i) loweralkyl,

ii) amino,

iii) alkylamino,

iv) dialkylamino,

v) (alkoxyalkyl)(alkyl)amino,

vi) (alkoxyalkoxyalkyl)(alkyl)amino,

vii) aryl,

viii) arylalkyl,

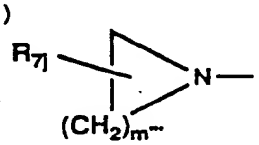
ix) aminoalkyl,

x) (N-protected)aminoalkyl,

xi) alkoxy,

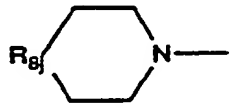
xii) substituted loweralkyl wherein the substituent is selected from alkoxy, thioalkoxy, halogen, alkylamino, (N-protected)(alkyl)amino and dialkylamino,

xiii)



wherein m''' is 1 to 5 and R_{7j} is hydrogen, hydroxy, alkoxy, thioalkoxy, alkoxyalkoxy, polyalkoxy, amino, (N-protected)amino, alkylamino, (N-protected)(alkyl)amino or dialkylamino; or

xiv)



wherein R_{8j} is O, S, SO_2, O=C or $R_{9j}N$ wherein R_{9j} is hydrogen, loweralkyl or an N-protecting group; and

2) Q_j is

i) C=O or

ii) CH_2,

with the proviso that X_j is N when R_{1j} is an N-protecting group;

(VII) $R_{54j}S(O)_2$- wherein R_{54j} is

1) amino,

2) alkylamino,

3) dialkylamino,

4) loweralkyl,
5) haloalkyl,
6) aryl,
7) p-biphenyl,
8) heterocyclic or

(VIII) $(R_{55j})_2P(O)-$ wherein R_{55j} is
1) alkoxy,
2) alkylamino or
3) dialkylamino;

A_j and L_j are independently selected from
(I) absent,
(II) C=O,
(III) SO_2 and
(IV) CH_2;

D_j is
(I) C=O,
(II) SO_2 or
(III) CH_2;

Y_j is
(I) N or
(II) CH;

R_{2j} is
(I) hydrogen,
(II) loweralkyl,
(III) cycloalkylalkyl,
(IV) $-CH_2-R_{10j}-(CH_2)_{q'''}-R_{11j}$ wherein
1) q''' is 0, 1 or 2,

2) R_{10j} is absent or R_{10j} is O, NH or S only when q''' is 1 or 2, and

3) R_{11j} is

i) aryl or

ii) heterocyclic;

Z_j is

(I) hydrogen or

(II) $-R_{28j}C(O)R_{29j}$, $-R_{28j}S(O)_2R_{29j}$ or $-R_{28j}C(S)R_{29j}$ wherein

1) R_{28j} is

i) NH,

ii) $-N(R_{200j})-$ wherein R_{200j} is loweralkyl or benzyl or

iii) CH_2 and

2) R_{29j} is

i) alkoxy,

ii) benzyloxy,

iii) alkylamino,

iv) dialkylamino,

v) aryl or

vi) heterocyclic;

R_{3j} is

(I) hydrogen,

(II) loweralkyl,

(III) loweralkenyl,

(IV) cycloalkylalkyl,

(V) cycloalkenylalkyl,

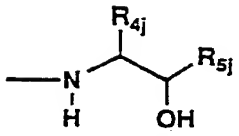
(VI) alkoxyalkyl,

(VII) thioalkoxyalkyl,

(VIIII) (alkoxyalkoxy)alkyl,
(IX) (polyalkoxy)alkyl,
(X) arylalkyl or
(XI) (heterocyclic)alkyl;

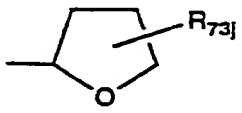
n''' is 0 or 1; and

T_j



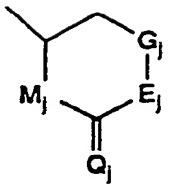
wherein R_{4j} is
(I) loweralkyl,
(II) cycloalkylalkyl or
(III) arylalkyl; and

R_{5j} is
(I)



wherein R_{73j} is loweralkyl,

(II)



wherein

1) M_j is
   i) O,
   ii) S or
   iii) NH;
2) Q_j is
   i) O or
   ii) S;
3) E_j is
   i) O,
   ii) S,
   iii) CHR_{61j} wherein R_{61j} is loweralkyl,
   iv) $C=CH_2$ or
   v) NR_{18j} wherein R_{18j} is
      a) hydrogen,
      b) loweralkyl,
      c) hydroxyalkyl,
      d) hydroxy,
      e) alkoxy,
      f) amino or
      g) alkylamino;

and

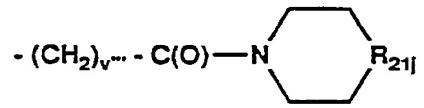
4) G_j is
   i) absent,

ii) CH_2 or

iii) NR_{19j} wherein R_{19j} is hydrogen or loweralkyl,

with the proviso that when G_j is NR_{19j}, then R_{18j} is loweralkyl or hydroxyalkyl;

(III)



wherein

1) v''' is 0 or 1 and

2) R_{21j} is

i) NH,

ii) O,

iii) S or

iv) SO_2; or

(IV) a substituted methylene group;

or a pharmaceutically acceptable salt, ester or prodrug thereof.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/05248

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61K 37/00
U.S. Cl.: 514/2 530/323

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	514/2; 530/323

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

APS, CAS on line: Renin inhibitors and (vascular or diabetes). Structure Search

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y, P	US, A, 4,812,555 (RADDATZ) 14 March 1989 See column 1 lines 61-69 and column 2 lines 1-9	1-8 and 10-17
Y	The New England Journal of Medicine, volume 312, No. 22, page 1412, published May 30, 1985, J.A. Luetscher, "Increased Plasma Inactive Renin in Diabetes Mellitus." See page 1415 column 2 lines 3-7 and page 1416 column 1 lines 1-5.	1-8 and 10-17

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

07 MARCH 1990

Date of Mailing of this International Search Report

22 MAR 1990

International Searching Authority

ISA/US

Signature of Authorized Officer

ZOHREH A. FAY

Form PCT/ISA/210 (second sheet) (Rev. 11-87)